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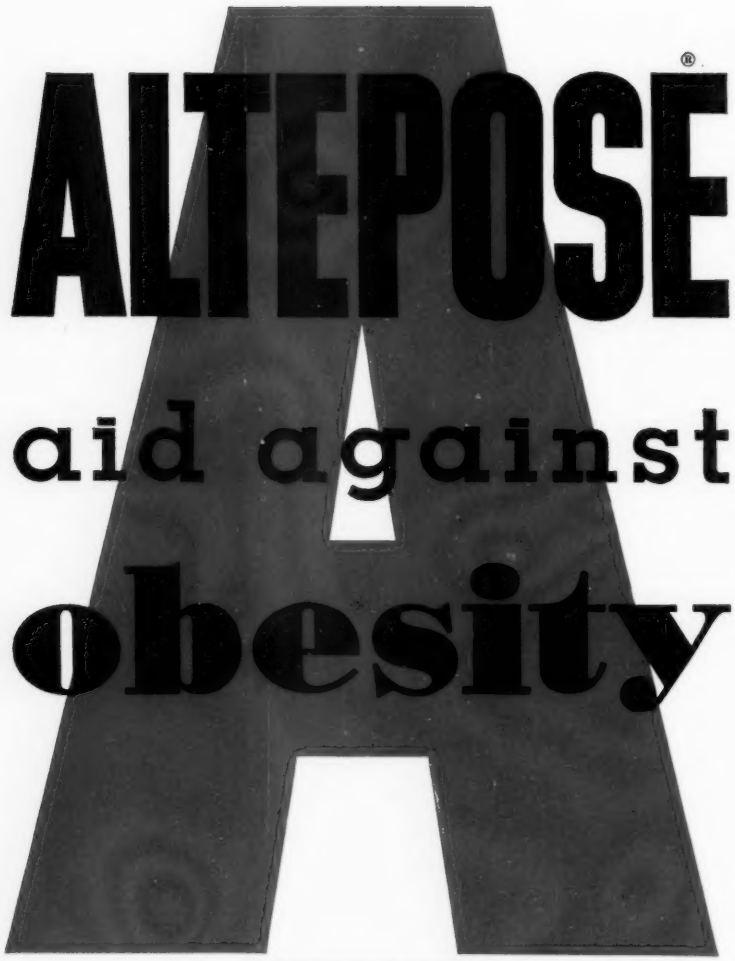

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Malpractice and Its Prevention

LOUIS J. REGAN*

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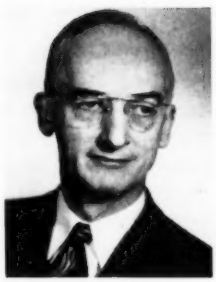
What constitutes malpractice, how it may be avoided and what to do if confronted with a malpractice action are discussed in this article. Illustrative cases are given.

You may ask, "Why should I be interested in malpractice?" In answer, I would say that you should be interested for the following reasons:



L. J. REGAN

1. An unjust malpractice claim may eventuate from each professional contact you have.

2. The incidence of such claims has increased frighteningly during the past 20 years—to the point where almost 4000 are brought each year.

3. These claims have become so common that in some localities any patient with a less-than-perfect end result is a potential malpractice claimant.

4. The misunderstanding and ill will thus engendered threaten to destroy the prestige of the profession.

5. A physician in his lifetime sustains few shocks as great as that which he would experience if he were sued for malpractice. It is quite a different matter to be sued for malpractice than for allegedly having driven an automobile in a negligent manner. In a malpractice action your professional reputation and integrity are being assailed. Yet it is a fact that you are now more likely to be sued for malpractice than for negligent driving.

Theoretically a doctor should be able to avoid accusations of malpractice if he cares for every patient with meticulous attention to the requirements of good medical practice. Actually, as the most unprejudiced analysis will disclose, the great majority of malpractice claims made and suits brought are without meritorious foundation.

Malpractice is frequently defined as the failure on the part of a physician to fulfill his legal duty to his patient, with the result that the patient suffers an injury.

A physician undertaking to render professional care to a patient represents by implication that he possesses skill and knowledge equal to that commonly possessed by other reputable physicians in the locality. The law also requires that in treating his patient he exercise the degree of care, attention, diligence and judgment commonly exercised by other practitioners in handling similar cases. It should be noted, too, that one who calls

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Presented at the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

himself a specialist must possess and exercise the skill and care of a specialist.

Actionable malpractice, therefore, may be said to be the doing of something which the ordinary practitioner would not do or the failing to do something which he would do in a similar case.

The standard of practice which the physician must meet does not require him to possess or to exercise the highest or even a high degree of skill and care. Further, whenever reputable physicians might differ in method of treatment, no liability devolves upon a physician who, in the exercise of his best judgment, selects a recognized procedure, even if it later appears that he might have chosen another and, in retrospect, a better method.

If he has fully met the standard of practice the physician is not liable for failure to cure a patient or for untoward results that follow treatment. He is not an insurer of the results of his treatment unless he makes himself one by his special promise or contract.

One who follows malpractice litigation cannot escape the conclusion that the lay persons involved tend to exaggerate the skill and capacity of physicians in general and constantly suggest that an unsatisfactory outcome is indicative of lack of skill or of negligence on the part of an attending physician. This attitude, which unfortunately is also not uncommonly reflected by jurors, has no legal sanction, of course. If the law supported such a view, a physician would be obliged at his peril to cure the patient, and every tombstone would be a perfect foundation for an action.

The professional group cannot escape the responsibility for doing everything in its power to eliminate instances of actual malpractice. The overwhelming majority of physicians faithfully and unselfishly meet the demands and obligations of their calling. The acts of the ignorant, the greedy, the callous few must not be permitted to destroy the merited esteem in which the profession as a whole is held.

Any patient may sue any physician who has cared for him. No one is immune and no known course of conduct will unfailingly ward off the unjust suit. *Caveat*, doctor! It is evident, however, that the patient who has a friendly feeling for his physician and who believes that everything possible has been done for him is not likely to sue for malpractice, even though results of treatment are unsatisfactory.

It is clearly important to try to establish and to maintain a warm relationship with every patient. The patient should be brought to recognize and appreciate the doctor's sincere and intelligent interest in his welfare. The relationship should be founded on fair-dealing, diligent attentiveness and reasonable and honest disclosure, so that the patient feels a secure confidence in his attending physician. The patient must be made to feel that the physician's interest is in him as an individual. This essential, over-all consideration should go beyond the study and treatment of a particular organ, system or disease. From the point of view of legal entanglement it might be said that the current practice of medicine threatens to become too objective, too focused.

Inevitably some of us are going to be sued for malpractice. The wise physician will recognize his vulnerability. He not only will take every possible precaution to safeguard himself but he also will endeavor to be always in the strongest possible position for successful defense when and if he is unjustly sued.

Let us briefly consider some other aspects of malpractice prophylaxis.

As a first point, a physician is under no obligation to accept a patient. He may arbitrarily refuse to undertake the care of any and every person if he wishes. But when the relationship of physician and patient is established it can be terminated only in certain ways if the physician is to avoid liability. He is not freed of responsibility simply by staying away from the patient. In the absence of special contract or notice, he must continue to give the needed care and attention until his services are no longer necessary, unless he is discharged sooner by the patient or unless he withdraws from the case by advising the patient of his intention and allowing the patient a reasonable time to fill his place.

Particular attention must be called to the large number of malpractice claims which may be generally classified as "insufficient treatment cases." Such cases are to be found in every field of medical practice. To illustrate: There are cases alleging the failure to make a blood count, a Wassermann, a pregnancy test, a culture, a smear, a urinalysis, a stool examination or an x-ray; the failure to make a complete diagnosis or to observe a reasonably determinable condition; the failure to utilize an indicated prophylactic measure, and the failure to give instructions, to follow up the original treatment or operation or to institute measures to protect contacts, etc.

The failure to use the x-ray at all or the failure to make sufficient use of the x-ray has been the chief allegation in many malpractice actions. Whenever a fracture is present but not diagnosed and no x-rays are taken, the conduct of the attending physician is likely to be condemned as not coming within the standard of good practice. Whenever a poor result—deformity or limitation of motion—occurs, the defense is immeasurably strengthened by the possession of a series of x-rays taken at intervals during the progress of the case. X-ray records, as well as the entire case record, should be carefully preserved beyond the time during which a malpractice action may be brought.

The statute of limitations provides the time after which specified actions may not be brought. The time provided varies in the several states; physicians should inform themselves of the situation in their own states.

The precipitating cause of a majority of all malpractice actions is found in the unwise comments or the critical remarks of physicians themselves. Commonly it is criticism by a succeeding physician of the work of his predecessor on the case. Various authorities have estimated that 50 to 80 per cent of all the unjust suits for malpractice would be eliminated if destructive, unethical criticism could be stopped. Legitimate criticism can rest only on full knowledge of the facts as gathered from the physician who treated the patient as well as from the patient.

Many malpractice actions are brought as the result of some unwise statement made by the attending physician or by his partner, assistant, or office nurse to the patient or to a friend of the patient. Care should be taken to avoid making any remark constituting an "admission" of fault or one which may be construed as such. The physician should never write a letter or make any statement with reference to a malpractice claim, except upon the recommendation of his legal advisor. Immediately upon learning of even the possibility of suit he should consult his attorney.

Consent for operation must always be secured. Any adult in a clear state of mind may authorize operation upon himself. Oral consent may be considered sufficient; but, because of the difficulty in proving that it was given, the physician should invariably require a written authorization. If the patient is a minor consent is to be obtained from parent or guardian; if the individual is mentally incompetent the consent of the guardian is required.

In an emergency which justifies immediate action for the preservation of the life or health of a patient and in which it is not practicable to obtain his consent or the consent of anyone authorized to speak for him, it is the duty of the attending physician to perform, without specific consent, such operation as good surgical practice demands. In such a circumstance consultation should be had to corroborate the emergency.

If sterility is likely to result from the surgery which is contemplated, explanation of that probability should be made and a signed authorization obtained from both spouses. It should be borne in mind that it is hazardous to sterilize any person except upon a positive medical indication. Further, there should be no promise or guarantee that the patient will be sterilized as the result of the procedure undertaken.

The individual physician must secure consent to perform a postmortem examination. This also should be in writing and sufficiently comprehensive to allow the removal and taking away of parts if such is contemplated.

Since a physician may become liable for

the acts of another, it is vitally important that he exercise care in the selection of assistants and in the delegation and supervision of functions assigned to them. Further, he should frequently check the condition of his equipment and make use of every available safety installation.

Of all the measures available to the physician to safeguard himself, two are of the greatest importance: (1) the maintenance of good medical case records and (2) the constant use of protective consultation.

It is desirable that an attending physician ask himself from time to time what he would wish to have in the record of the case under treatment should he later be called upon in court to justify his conduct of the case. The trend of the cases in recent years indicates that it is extremely unwise to pursue a course of treatment in itself hazardous or capable of producing harmful effect without securing a written statement from the patient or from someone legally responsible for the patient—a statement which clearly expresses understanding of and consent to the special treatment. Furthermore, if a patient discontinues treatment before he should or fails to follow instructions, the record should show it. A good method is to file a carbon of the letter sent to the patient advising him against the unwise course. Proof of the mailing of the original should be appended.

The physician should exercise tact as well as professional ability in handling his patients. The attentive physician may early sense some unsatisfactory and disturbing undercurrent which, by the institution of protective measures, may be prevented from developing into something much more unpleasant. It is urgently recommended that if the patient is not doing well, consultation should be *suggested;* if the patient is complaining unduly or if the family's attitude indicates dissatisfaction, consultation should be *demanded*. In any case the use of a consultant affords great protection against a malpractice claim.

A few other important malpractice prophylaxis "commandments" are mentioned:

1. The physician must keep abreast of progress in his profession but he must not experiment in the treatment of his patient.

2. He should refrain from promising too much to the patient.

3. He should advise his patients of any intended absence from practice and should recommend or make available a qualified substitute.

4. He should keep inviolate all confidential communications.

5. He should secure legal advice if he is called to attend a coroner's inquest as a witness in a case in which he has been in professional attendance.

6. He should realize that it is hazardous to telephone a prescription and that it is wise to preserve a carbon copy of every prescription.

7. He should make every effort to avoid any situation which might give color to an accusation of undue familiarity. The only way to avoid claims of this sort seems to be to have a third party present during all examinations of patients of the other sex.

In the final analysis it is the physician himself who is responsible for the continuing existence of the vicious malpractice situation. He has generally been content to pay his professional liability insurance premiums and thereafter to sit back complacently, doing nothing until he becomes the target for a malpractice claim. The physician must realize that his money payment is only a part of his insurance premium—that the much more important part is his contribution of time and study and the putting into effect of all possible measures to safeguard himself and his colleagues.

I have said that the professional group must accept its responsibility to do everything possible to prevent the occurrence of actual malpractice. To a degree it can achieve this end by reasonable policing of its members; by offering continual instruction in malpractice prophylaxis; by maintaining a functioning claims-prevention service; by making available—when indicated—lectures, clinics and refresher courses, and by otherwise encouraging the raising of standards of practice.

A well founded and efficiently administered state or county association malpractice pro-

gram tends to raise medical standards, to improve medical public relations, to control—to a degree—those physicians who are inclined to overcharge patients and those physicians who need special attention to keep them up to the mark, and to eliminate the unprincipled and unethical practitioner.

There is no relationship outside of the family which is so personal and so intimate as that of the physician to his patient, no other relationship in which the character, integrity and conscience of one party are so important to the welfare of the other.

There will be few instances of actual malpractice when practitioners fully accept their responsibilities and when their moral and ethical standards are consistently high. However, adherence to the highest possible moral and ethical standards and the constant exhibition of the required standard of skill and care will not immediately eliminate the nonmeritorious claim on the unjustified suit. Only when practitioners understand fully how to protect themselves under the law will there be fewer instances of injury to physicians resulting from unfounded charges brought by ignorant, misguided or malicious patients.

Illustrative Cases

Following is a small portion of the cases dealt with in a 15 day period during August 1951, by a functioning county medical association claims prevention program.

1. Doctor B. said that he had a patient referred to him by the local prosecuting attorney's office to determine if the patient should be recommended for probation. The doctor stated that it was his opinion that the man was a paranoic with sexual psychopathic tendencies and that the patient should be committed for further psychopathic study. The doctor desired to know whether he could be sued for libel if he incorporated this in a report to the Probation Department. He was advised to act in accordance with the instructions of the court and that he could so do without liability.

2. Doctor E. B. reported that he had operated on an Egyptian national who had urologic difficulties and that, following the operation, the man ejaculated into the bladder. The patient desired to have a letter stating that he was still potent and procreative. He explained that he wanted this letter to exhibit in his own country to prove that he was not impotent. The doctor was advised to supply the patient with the requested letter.

3. Doctor C. stated that he had as a patient a girl of 17 with a marked mental deficiency who lived at home and whose parents, fearing that she might possibly become pregnant, desired that she be sterilized. History showed much menstrual pain but no abnormal physical findings. The doctor was advised that there did not seem to be sufficient grounds to justify the sterilization of this patient. It was suggested to him that if sterilization was necessary because of her mental condition it was desirable to have her committed (Eugenic Sterilization Statute).

4. Doctor H. asked if her nurse could give hypodermic injections to patients in her, the doctor's, absence. The doctor was advised that a registered nurse could do any and all of those things that she is ordinarily trained to do in an accredited school of nursing, provided that she does those things upon the direction or prescription of a licensed physician and upon his patients. If these requirements are met, the doctor's presence is unnecessary.

5. Doctor K. said that he had been treating a patient during pregnancy. The amount of the fee had been discussed and arranged; however, each check given in payment thereon bounced. The doctor desired to know if he could withdraw from the case. He was advised that he could do so and a letter was dictated to his secretary which was to be sent to the patient.

6. Doctor H. D. is the plant physician for a company which employs minors. He reported that no anticipatory consents were obtained from the parents of the minors and that surgery was being performed at the company's request without any specific authorization. It was suggested that the doctor submit the problem in writing so that an opinion might be prepared which he could show to the company officials. A special consent form was

thereafter prepared to be signed by the parents of the minors at the time they entered employment.

7. Doctor O. said that he had taken x-rays of a patient who now was demanding the x-rays and threatening to sue if they were not turned over to him. The doctor was told to inform the patient that the x-rays were a portion of the case record and would be retained as such; that, however, they were available to be viewed by the physician who was now caring for him.

8. Doctor S. reported he had been treating a Navy nurse who was A.W.O.L. from the Navy and that a Navy investigator was seeking information regarding her care and treatment. The doctor was advised not to give out any information concerning this patient; that the confidential relationship protected her as much as any other patient.

9. Doctor H. S. telephoned to state that a 16 year old girl in one of the families he treated had had sexual relations with her 19 year old boy friend and that, on request of the girl and without the knowledge of her parents, he had examined her to determine if she was pregnant. The doctor wanted to know if he was obliged to tell the parents. He was advised that a doctor may not, except in emergency, examine or treat a minor without authorization of parent or guardian; that the examination constituted a technical assault; that, in the circumstances, he would have a duty to advise the parents but it was to be recognized that he had exposed himself to potential liability.

10. Doctor I. reported that as he sutured a laceration on the thigh of a 3 year old child, the needle had broken, a portion of it remaining in the tissue. The family had been immediately advised. He further stated that arrangements had previously been made for the child to have a tonsillectomy the next week and that the family was agreeable to having a search made for the foreign body at the time of the tonsillectomy. The doctor was advised that the arrangement was approved on the basis of bringing in a consulting surgeon to remove the needle. He was further advised to send the following letter to the child's parents:

> Dear Mr. and Mrs. Blank:
>
> During the suturing, yesterday, of the laceration on Billy's leg, the needle broke and a portion remained in the tissue. You were immediately advised of this accident.
>
> As I told you, after preliminary search, I was unable to recover the broken piece without anesthesia and incision, and recommended that localization studies be made prior to undertaking definitive search.
>
> At your request and responsibility, arrangements have been made to have Doctor Surgeon search for the foreign body while Billy is under anesthetic for this tonsillectomy.
>
> Yours very truly,

11. Doctor T. W. called, stating he had operated on a nurse for a femoral hernia. Shortly thereafter he observed paralysis of the quadriceps extensor. Under advice, the patient was informed of the apparent injury; the next morning an operation was performed by a neurosurgeon. The severed nerve was found and continuity was restored. There were no costs except the hospital bill and the salary of the nurse during the period of disability. Final result was good, and a release was obtained.

12. Doctor W. L. reported poor results in the treatment of a Colles' fracture. No x-rays had been taken. Under advice, and with cooperation of the hospital clinic and clinic physicians, the patient, who was friendly, was hospitalized as a clinic patient. Open reduction was done with good result.

13. Doctor W. M. called to report that tubal sterilization had been done three months before, at the time of a second cesarean on an Rh negative woman; that the woman was now in his office claiming that while he had guaranteed that she would be sterile she was, in fact, pregnant. The doctor was advised to call to the patient's attention that the terms of the authorization for operation, signed by her and by her husband, specifically excluded guarantee or warranty of sterility.

Management of Patients Suffering from Difficulty in Swallowing

WITH SPECIAL REFERENCE TO CARDIOSPASM

PORTER P. VINSON*

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Advances in surgery have tempted thoracic surgeons to perform operations for treatment of nonmalignant lesions of the esophagus that can be managed effectively by more conservative measures. Unnecessary operations for the treatment of cardiospasm are apparently now being employed more frequently. A plea is made for dilation of the cardia rather than for the use of more radical operative treatment.

P. P. VINSON

REMARKABLE developments have occurred during the past 15 years in the surgical approach to the intrathoracic organs. The esophagus has, of course, shared in these developments, which have come about through three main factors: (1) improvement in surgical technic, (2) use of antibiotics and (3) more liberal use of whole blood transfusions. It was hoped that as a result of this progress we would be able to report more favorable results in the treatment of esophageal lesions, especially carcinoma. I am sorry to say that insofar as my personal experience is concerned I have been greatly disappointed in the end results of surgical excision of cancer of the esophagus. Esophageal carcinoma metastasizes before it has given rise to local distress in the esophagus, and it has a very high degree of malignancy. According to Dr. Broders' classification esophageal carcinoma is either grade 3 or 4, which makes it a rather difficult problem even though the lesion may appear to be well localized.

An unfortunate result of the advancements in the surgical approach to the esophagus has been the fact that thoracic surgeons have undertaken the surgical treatment of benign lesions which in most cases had been satisfactorily handled by other means prior to the improvements in thoracic surgery. I believe a lot of unnecessary resections of the esophagus have been done in cases of benign stricture, and also various plastic short-circuiting operations in cases of cardiospasm. Cardiospasm is very effectively handled by ordinary mechanical dilation, and although the mortality rate has been reduced for surgical procedures involving the esophagus, any operation on the esophagus still carries a rather formidable amount of surgical risk. There has been increasing improvement in the mechanical treatment by means of the esophagoscope and other methods, and the majority of benign esophageal lesions can now be handled with a minimal amount of risk.

Since 1923, in my experience and in that of my associates, there has been no fatality associated with the treatment of cardiospasm. This treatment group represents probably 1500 to 2000 cases in which dilation of the esophagus was done. There is very little mor-

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Presented before the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

bidity associated with dilation, the patients are rarely hospitalized and the functional results are excellent. About 75 per cent of all patients with cardiospasm can be completely or almost completely relieved by dilation of the cardia; the other 25 per cent are so markedly improved that they do not require any more radical treatment. Consequently it does not seem quite right that thoracic surgeons should recommend a formidable operative procedure in which the mortality rate is around 10 to 15 per cent and the functional results are not as adequate.

I do not know why dilation relieves cardiospasm, nor do I know the cause of cardiospasm, but I do know from years of experience that mechanical stretching of the cardia will relieve the symptoms of cardiospasm and that dysphagia rarely recurs. I know also that whenever a patient has had a dilation of the cardia with an expanding dilator and has not been relieved of his symptoms the chances are the cardia was not stretched effectively. In such a case the first question I ask is, "Did your doctor use a guiding thread in introducing the dilator into the cardia?" Invariably the answer will be no. If a guiding thread was used, I then ask the patient whether he had any pain when the dilator was expanded and the cardia was stretched. If he says he had no pain, then I know the dilator was not in place. You cannot expect to obtain the desired results by expanding a dilator in the esophagus or in the stomach unless it is expanded at the point of constriction, and the dilator can slip very easily into the stomach or into the cardia, even in the hands of those who have had extensive experience with this procedure.

For dilation, a 60 French sound is used. If that doesn't give the results desired, a hydrostatic dilator is used. The sound will be effective in about half the cases. If the hydrostatic dilator is required, it is passed down to the bottom of the esophagus with the thread relaxed, the thread is drawn taut, the dilator is advanced to the cardia and introduced, and then the dilator is distended and held just for a few seconds.

About a year ago a patient of mine, a doctor from Washington—a rather jittery sort of fellow—had cardiospasm with complete esophageal obstruction; he was not able to swallow water. He was able to swallow a thread, and then I dilated the cardia. He went through all sorts of contortions when the dilator was expanded, and I thought certainly that I had stretched the cardia effectively. After the dilation he said, "Doctor, I'm sorry, but it really didn't hurt at all. I was just a little nervous." The second time the dilation was done, I said, "Now, Doctor, I don't mind how much you squirm, but will you just raise your hand when this thing begins to hurt you so I will know that you are having pain and that the dilation is effective." When the time came he raised his hand and I thought the cardia had been dilated. Afterward he said, "Doctor, I'm awfully sorry; I really shouldn't have raised my hand because it didn't hurt." So the third time we agreed on this thing and he got an effective dilation. Afterward he remarked, "That was different from the others." He was completely relieved and has remained so ever since.

The mere motion of putting a dilator into the esophagus and distending it does not indicate that the cardia has been dilated, and unless this is done you cannot expect the patient to be relieved of his cardiospasm.

Thoracic surgeons have said to me, "This patient has had numerous dilations of the cardia and hasn't obtained any relief, and therefore we recommend surgery." I have seen only 2 patients in my total experience since 1919 who have not been relieved of their cardiospasm by dilation with a hydrostatic dilator. Both these patients had marked dilation and angulation of the esophagus, and as a result the dilator had not gone into the cardia. In both cases the procedure which was done consisted of opening the stomach from below and dilating the cardia manually; this is preferable to a plastic operation on the cardia, which may result in a cicatricial stricture and more difficulty than the patient had with cardiospasm.

There are certain benign lesions in the esophagus that require surgical treatment. For instance, rupture of the esophagus caused

by a foreign body or instrumentation is readily handled by surgery. There are other benign lesions that may be treated surgically, but for the most part the treatment of cardiospasm should be the older, approved method of mechanical dilation of the cardia, that of using a guiding thread to introduce the dilator into the cardia.

Illustrative Cases

I would like to describe briefly several cases which illustrate many of the points already emphasized:

1. A woman developed a stricture and almost complete necrosis of the stomach as a result of swallowing a solution of zinc chloride. This had been given to her for use as a vaginal douche. Instead of following the directions for diluting and using the solution, she took some of it by mouth with suicidal intent, with great damage to her stomach. Being a slow-acting escharotic, the zinc chloride did not affect the esophagus but did damage the stomach. A total gastrectomy relieved her of her difficulty. An esophagojejunostomy was performed and this girl has had an excellent result. No dilation, of course, could have been effective in her case.

2. A simple stricture of the esophagus resulted when a girl swallowed lye, and an enthusiastic thoracic surgeon decided she must have an operation. Her stomach was brought up into the thorax, connected above, and practically all of the esophagus was removed. Afterward this girl was utterly miserable because of the hernia of the stomach up into the thorax. In a patient with cancer, this type of operation can be done, but I think that it is entirely too formidable and radical a procedure for a case of benign stricture of the esophagus that can be relieved by simple dilatation of the esophagus. Unless it is a life-saving procedure, as in cases of carcinoma, that type of operation is not indicated.

3. In a case of cardiospasm, a plastic operation was done on the cardia in an attempt to relieve the condition, resulting in a cicatricial stricture which was more serious than the patient's original difficulty and from which we could offer him little relief.

FIGURE 1. Marked dilation and angulation of esophagus.

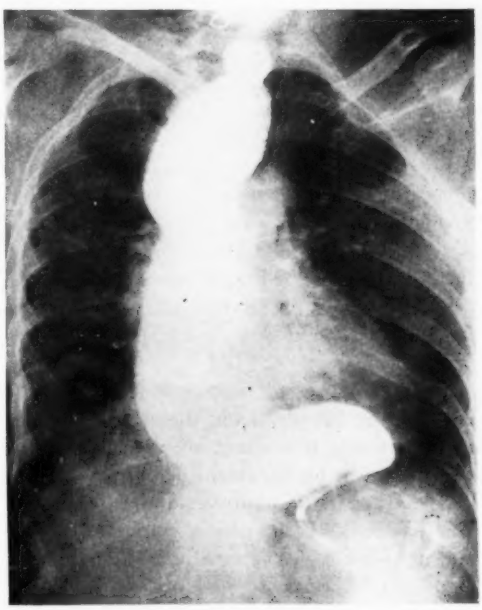

FIGURE 2. Cardiospasm of 30 years' duration, with marked angulation and dilation of esophagus.

4. I have seen 2 cases in which there was so much angulation and dilation of the esophagus that even with a guiding thread I was unable to introduce a dilator into the cardia (Figures 1 and 2). Both these patients obtain-

ed very satisfactory results when the cardia was dilated from below. I might add that the guiding thread is very helpful to the surgeon in locating the cardia from below.

5. It formerly was thought that the sympathetic nervous system had something to do with the production of cardiospasm. That theory probably is fallacious. Cardiospasm probably is entirely on a vagus basis, and the sympathetics play no part in the innervation of the esophagus or, rather, the abnormal innervation, nor in the production of cardiospasm. One of my patients had a sympathectomy for relief of pain, but without success. We could not relieve her pain by dilation.

6. Numerous attempts were made to dilate the cardia of a woman who had cardiospasm and difficulty in swallowing. When these attempts were unsuccessful she was sent to a surgeon and an operation was done. Following the operation she had just as much difficulty as before. She was sent to me and I approached the problem with fear and trembling, not knowing how much scar tissue was present nor just what I could do about it. A simple hydrostatic dilation of the cardia gave relief. I was unable to find out just what type of surgical procedure had been performed, but at any rate this woman had undergone a prolonged intrathoracic operation for the treatment of cardiospasm, an operation which was ineffective, and was then relieved by a single hydrostatic dilation of the cardia.

7. A man who had obstruction at the cardia was told by his physician that he had a cancer and would live about six months. A tube was placed in his stomach. About six months later he began to improve, and when I saw him I asked, "Well, what's your story?" He told me what his physician had told him, and then said, "I came to find out why I'm not dead." He was found to have cardiospasm, and one dilation of the cardia gave him relief. We removed the tube and the gastrostomy closed up.

8. A New York society woman had had cardiospasm and a gastrostomy for 18 years. When she went to social functions she would eat like everybody else and then go out and empty her esophagus and take her feeding by tube. After 18 years of this, she had a hydrostatic dilation of her cardia and obtained relief.

9. There have been reports of cardiospasm in infants and of relief obtained by the passage of a stomach tube. As you know, the innervation of a child's esophagus, or any other part of a child, is very uncertain at birth, and it has always been my belief that these cases of congenital cardiospasm are not cardiospasm at all. One case provided me my opportunity to prove to my own satisfaction that this condition is simply one of the disturbances in early innervation of the esophagus. This child had difficulty in swallowing, with regurgitation. The film showed a dilated esophagus with obstruction to the cardia. Several procedures were discussed in regard to treatment, and I said, "Let's not do anything; let's see what happens." The child recovered spontaneously without treatment. I have never believed that the passage of a stomach tube in a child or anybody else will relieve cardiospasm.

10. A girl was sent to a tuberculosis sanatorium because she had a cough and because after meals she coughed until she vomited. A chest x-ray showed a large mediastinal shadow and she was sent to me for diagnosis of a mediastinal tumor. The tumor proved to be a large esophagus filled with food, and one dilation dispelled her tuberculosis and her tumor.

11. In an attempt to force food through his cardia, one patient with cardiospasm had a spontaneous pneumothorax (Figure 3). We dilated his cardia and he obtained relief.

12. Loss of weight was a feature in one case of cardiospasm. This woman's weight dropped from 250 to 117 pounds (Figure 4). She had complete obstruction of her cardia. Despite the fact that she was unable to swallow a drop of water through her cardia and that she was markedly dehydrated, she got a thread down in 24 hours, we dilated her cardia and she was completely relieved. In six months she had regained 50 pounds and didn't want to gain any more.

13. Loss of weight also occurred in an-

other case, that of a female patient, a bootlegger by trade. (Of course, a psychiatrist would tell us that fear of the revenue officer caused the cardiospasm.) We dilated her cardia, and two and a half years later her husband came to see me. I asked, "How's your wife?" "Doctor," he said, "she couldn't get through that door." He told me that after her dilation she had weighed 105 pounds and that she now weighed 209. She had doubled her weight and I suppose the revenue officers were still after her.

14. A complication of cardiospasm is illustrated by the case of a girl who was under the care of a psychiatrist. Every week for a year she had a session with him and he would question her and then the next week she would go back and he would say, "My dear girl, you didn't answer that question the same way last week." Then she would become confused and proceed to be a real candidate. After a year of this she finally had her cardia dilated and has been well ever since.

15. While in the Army, a young man began to have difficulty in swallowing and was sent to a psychiatrist, who said, "Now, let me find out something about you. Let's see, your mother and father were divorced and that is the background for the whole thing." This boy continued to have trouble and finally when he entered medical school after he got out of the Army he came to see me one day. He apologized for coming in because he knew it was "all nervous," but said, "The thing that bothers me is that I know it's 'all nervous,' but I'm getting disturbed about strangling at night; I'm afraid I'll get a lung abscess or something." I said, "Well, you might," and we dilated his cardia and he was completely relieved.

16. One of my old friends brought a patient to me from Washington, and very apologetically told me that he hated to dump this girl in my lap but that the surgeons had told him nothing could be done short of surgery. She had a bleeding, perforating duodenal ulcer and he was sure an operation couldn't be done. To make a long story short, the ulcer was resected, the cardia was easily dilated and she is perfectly well.

FIGURE 3. Cardiospasm with unusually complete filling of esophagus with barium mixture. Spontaneous pneumothorax on left following attempts to force food into stomach.

FIGURE 4. Cardiospasm in a woman who lost 133 pounds in weight. After dilation with a hydrostatic dilator, she regained 50 pounds.

17. A young man had undergone innumerable attempts to dilate his cardia. When we gave him a thread to swallow, he was perfectly disgusted: "Do you expect that to help me after all these things I have had put down my esophagus that haven't helped me at all?"

18. Diffuse spasm is very difficult to treat, and we have not been successful in many cases in providing relief (Figures 5 and 6).

FIGURE 5. Diffuse esophageal spasm.

FIGURE 6. Diffuse esophageal spasm.

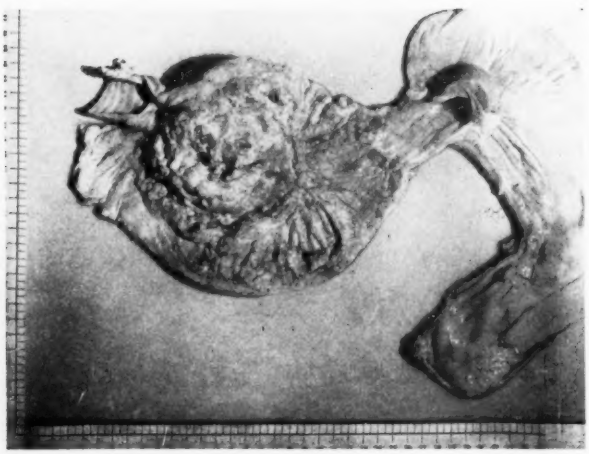

FIGURE 7. Cardiospasm of 35 years' duration; later development of carcinoma in upper third of esophagus.

Dilation sometimes is effective, and the only other alternative that I know of is gastrostomy. We have had 2 or 3 patients with diffuse esophageal spasm in whom we have had to do gastrostomies; the esophagus would close up completely and you could not get anything through. So far as I know, the thoracic surgeons haven't tackled these cases yet. I wish they would; I would like to see what would happen, because we cannot help them.

19. I don't think cardiospasm is the causative factor of one of the conditions which may occur in cases of cardiospasm, but I thought you might be interested in a patient who had had cardiospasm for 35 years and who later developed carcinoma in the midportion of the esophagus (Figure 7). His cardiospasm had been relieved by hydrostatic dilation, and he then began to have hemorrhages from the esophagus. We finally discovered a carcinoma to be responsible for the bleeding.

The Effect of the Ductless Glands on Growth and Development

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The endocrine glands which affect skeletal growth and development are the anterior pituitary, thyroid, gonads, adrenal cortex, pineal, thymus and parathyroids. Study of osseous development and skeletal variations aids the understanding of endocrine activity and the diagnosis of endocrine disorders.

A. A. WERNER

THE endocrine glands which affect preadult growth and development are the anterior pituitary, the thyroid, the gonads, the adrenal cortex, the pineal, the thymus and the parathyroids. Of these glands the effect of the adrenal cortex, the pineal and the thymus upon growth are of minor importance when compared with the influence of the anterior pituitary, the thyroid and the gonads. Adrenocortical and pineal disturbances affecting growth are rare. Abnormal conditions attributable to thymus dysfunction are more frequently seen than are those of pineal origin. The condition known as status thymicolymphaticus can probably be regarded as the indication of an inherent lowering of the intensiveness of the chemical and physical processes concerned in cell growth and consequently in tissue development. The parathyroids exert their influence in the deposition and mobilization of calcium and phosphorus in the osseous tissue. Since the adrenal cortex, the pineal and the thymus seemingly affect osseous growth only occasionally and have not the significance of the first three in influencing skeletal growth, they will not be discussed further.

For a thorough study of osseous development at any age it is necessary to have roentgenograms not only of the hands and wrists but also of other osseous structures, such as the epiphyses of the shoulders, scapulas, elbows, knees, ankles and feet. During the course of growth and development of the hands and wrists, including the lower ends of the ulnas and radiuses, 21 epiphyses make their appearance and unite with the diaphyses, and eight carpal bones appear and develop.

There is sufficient difference between the time of appearance and the complete development and union of these osseous structures to make a study of roentgenograms of the hands for the interpretation of normal, advanced or delayed osseous growth very valuable. The bones of the hands and the wrists probably offer the most reliable osseous region for this determination when study of the entire skeleton is not practicable.

It is important to remember that the time and degree of osseous development varies

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EFFECT OF NORMAL AND ABNORMAL PITUITARY-GONAD FUNCTION ON SKELETAL GROWTH

TYPE	ANTERIOR PITUITARY GROWTH HORMONE	ANTERIOR PITUITARY GONADOTROPHIC HORMONE	GONAD FUNCTION *Estrogen and Androgen Effect*	EFFECTS ON MEASUREMENTS	TYPE OF INDIVIDUAL
1	Normal	Normal	Normal about 12 years of age	All measurements equal	Normal individual, tall or short
2	Normal	Early	Early	Upper measurement greater than lower; span less than height	Short and stocky
3	Normal	Hypofunction	Delayed or hypofunction	Upper less than lower; span greater than height	Eunuchoidism
4	Hypofunction	Hypofunction	Afunction or hypofunction	Generalized underdevelopment	Pituitary infantilism
5	Hyperfunction preadult	Normal	Normal	Measurements equal	Normal gigantism
6	Hyperfunction preadult	Normal	Normal or hypofunction	Upper less than lower; span greater than height	Eunuchoid gigantism
7	Hyperfunction postadult	Normal, later decreased	Normal, later decreased	Not influenced	Acromegaly
8	Hyperfunction preadult and postadult	Normal, later decreased	Normal, later decreased	Either equal or eunuchoid	Acromegalic gigantism

Thyroid function is considered as normal in these types. It could vary slightly but variations of thyroid function will be ignored here because we are only considering the influence of pituitary-gonad function on growth.

considerably in normal individuals and that this difference may be as much as several months in infancy, to one or two years at adolescence. Normally girls develop sexually earlier than boys, and with the onset of sexual development there is stimulation of closure of the epiphyses; therefore osseous development and epiphyseal closure may occur one or two years earlier in girls than in boys between the ages of 10 and 16 years.

It may be well before proceeding further to state which hormones of these glands affect osseous growth and development:

1. We are certain that the growth hormone of the anterior hypophysis is indispensable for growth to adult stature, a lessened amount of this hormone being the direct cause of an important group of endocrine dystrophies and an increased or excessive amount of the hormone the direct cause of overgrowth.

2. A normally functioning hypophysis is necessary for normal function of the thyroid, sex glands and adrenocortical tissue.

3. Knowing that normal hypophyseal function is essential for thyroid normality—normal thyroid development and function—it is conversely true that normal thyroid function is necessary for hypophyseal normality.

4. The gonadotrophic hormone (follicle-stimulating at least) of the anterior pituitary is necessary to initiate the function of the gonads, which in turn stimulate secondary sexual development.

The osseous changes which are attributable to decreased gonadal function during the period of skeletal growth do not include the flat bones which develop from their osseous nuclei. (Metacarpals and phalanges are long bones.)

Osseous Development

The mesoderm is the middle of the three layers of the primitive embryo. It is derived

FIGURE 1 *(left)*. Cartilage bones showing epiphyses. So long as these epiphyses are open, in the presence of growth hormone, the individual can continue to grow taller.

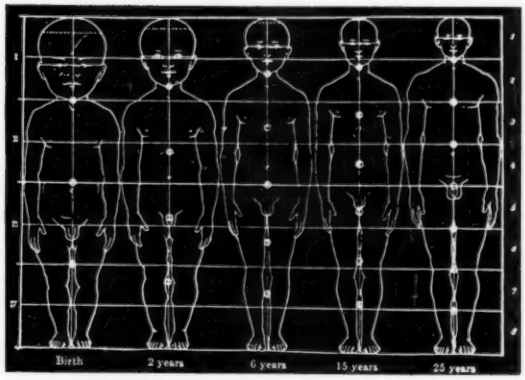


FIGURE 2 *(right)*. Composite picture of the normal proportions from birth to age 25 years.

from the ectoderm and the entoderm and develops into the skin and connective tissue structures, the bones, muscles, organs of excretion and the internal genitals. Thus cartilage and bone are of mesodermal origin. Bones may be classified according to their development as (1) membranous or secondary bones and (2) cartilage or primary bones.

Some bones develop independently of cartilage, such as the teeth and membrane bones. In the midst of the embryonic connective tissue, spicules of bone are formed and these unite to form a bone. The membrane bones consist of the bones of the face and the flat bones of the skull and various other portions of the bones of the head and the mandible. The remaining bones, known as cartilage bones, are formed by the deposition of perichondrial bone on the outside of a hyaline cartilage and of endochondrial bone upon the lining of excavations within the cartilage. The cartilage is not transformed into bone, although the matrix, in fact, becomes calcified and encased in bone. In the long bones this process of ossification produces a shaft of bone tipped with a mass of cartilage at either end. The shaft is the diaphysis and the cartilaginous end is the epiphysis. At various times after birth osteogenic tissue invades the epiphysis and gradually replaces its cartilage by bone. A layer of epiphyseal cartilage between the epiphysis and diaphysis and a layer of articular cartilage covering the joint persist longest (Figure 1).

Until adult life, in some bones, such as the femurs, the epiphyseal cartilages grow chiefly toward the diaphyses, and, as quickly as they form, the additions are replaced by bone. Thus, the epiphyseal cartilages are an essential provision for the lengthwise growth of bones. At various ages the different epiphyseal cartilages become completely calcified and united with the diaphyses, which precludes further growth in length of the long bones. After union of the epiphyses and diaphyses, the cartilages covering the articular surfaces are the only parts of the original cartilaginous structures that remain.

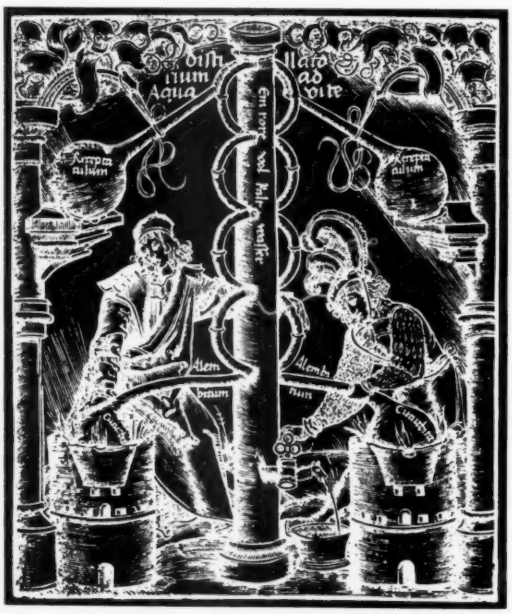
Strätz has compiled the normal proportions for the various ages from composites of a large number of normal individuals of both sexes to 25 years. It will be seen from the diagram (Figure 2) that at birth the upper measurement is five-eighths and the lower measurement is only three-eighths of the whole length. At 25 years of age the lower measurement (from the top of the symphysis pubis to the bottom of the heel with the foot at right angle to the leg) is equal to the upper measurement (from upper border of the symphysis pubis to the vertex). The head is one-fourth of the whole length at birth and at 25 years it occupies only one-eighth of the length. The lower extremities should grow more rapidly than the upper (torso and head) and at 25 years, if growth has been normal, they should equal each other and the span should equal the combined length of the upper and lower measurements; or one-half span

(from the center of the suprasternal notch to the tip of the middle finger with the arm outstretched) should equal either the upper or the lower measurement.

These statural proportions are dependent upon preadult osseous growth and osseous growth is influenced by the amount of hormone production, probably the quality of the specific hormones and the time of their elaboration in the growth period. (Nonendocrine conditions also have their effect, but to avoid complicating a sufficiently difficult problem they will be left out of the discussion.) When all possible variations of these three factors are considered, one must realize why we have such a multiplicity of skeletal types. However, the student need not despair of understanding this phase of endocrine activity for, when the causes of the more common types of skeletal variation are mastered, the reason for the intermediate degrees of growth can be easily understood.

The skeletal proportions of the individual are adaptable to diagnosis in two endocrine conditions, namely, preadult disorders of the anterior pituitary and of the gonads. The influence of the thyroid on osseous growth is probably indirect—by retardation of cellular metabolism in hypothyroid states.

The value of these measurements in adult life for diagnostic purposes is decreased except for the fact that one may know approximately the extent and type of glandular function of preadult life and this knowledge may assist in understanding conditions present in adult life.



From "The Distilling Book" by Brunschuygk which describes a phase of application of chemical methods to medical practice (1519).
(Courtesy, Brentano's Bookstores, Inc.)

Indications for Sympathectomy

JAMES L. POPPEN*

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Sympathectomy is discussed according to its effect on conditions relating to (1) the head and neck, (2) the extremities and (3) the thorax and abdomen. Indications for the operation are presented and the results of surgery evaluated. It is emphasized that each patient should be studied carefully before sympathectomy is done.

J. L. POPPEN

SYMPATHECTOMY can be of value in prolonging life or the usefulness of an extremity, and it also may relieve suffering. On the other hand, it is fair to say that the use of sympathectomy has been abused in the past and perhaps will be in the future. As one gains more experience, however, one realizes to some degree which patients may be benefited by the procedure and which may not.

We have had experience with over 2000 sympathectomies performed in 36 various conditions and, as you will see, in some it was of very little value.

It is best to divide the clinical entities into three divisions: (1) head and neck, (2) extremities and (3) thorax and abdomen.

Head and Neck

Thrombosis of the internal carotid artery—Thrombosis of the internal carotid artery usually occurs in the middle age group. It should be suspected in patients who have been well except for vague vascular symptoms of the lower extremities or perhaps angina pectoris, and probably in others who have had an episode of coronary infarction, sudden dizziness followed by unilateral numbness, and weakness of the upper and lower extremities lasting a few minutes only to recur in bouts before finally becoming permanent. In a few patients these symptoms subside completely even though complete occlusion has taken place, depending, of course, on the extent of the involvement.

If the thrombosis extends into the middle cerebral artery, complete and permanent disability will take place unless there is unusual collateral circulation between the posterior and middle cerebral arteries. Before the use of arteriograms by the closed method very few instances of thrombosis of the internal carotid artery were found except at autopsy or perhaps when an open arteriogram was made, at which time the artery could be directly examined. The arteriograms are characteristic. Since changes in the blood-brain barrier apparently take place during periods of anoxemia, I have refrained from performing bilateral arteriography on these patients. It is, of course, of help in deter-

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mining the prognosis to know whether adequate cross collateral circulation is present. On the other hand, it is possible to create further changes by injecting DIODRAST® into the contralateral side. Untoward symptoms following arteriography occurred only in such instances.

In cases in which the internal carotid artery is completely occluded, we have excised a segment of the artery and removed the superior and middle cervical ganglions as well as the carotid sinus. No immediate dramatic improvement has taken place in these patients except in the early cases. I believe that vasospasm of the cerebral circulation takes place, although it is fair to say that none of the methods which have been described as demonstrating this has been conclusive. From a practical standpoint, in patients who have been subjected to ligation of the internal carotid artery in the treatment of intracranial aneurysm, it has been demonstrated that constant procaine infiltration of the superior cervical sympathetic ganglion has been of merit. In 2 such patients, a few minutes after the injection of procaine was stopped, weakness of the contralateral side was noted; immediately upon interrupting the superior and middle cervical ganglions with procaine, normal function was restored. This seems to indicate at least that vasospasm is a definite factor. Single stellate blocks with 10 cc. of 1 or 2 per cent procaine are of little, if any, value in these patients except during an acute episode. I believe procaine should be given as a constant drip through a small inlying tube or by injecting 5 to 10 cc. every two hours so that a prolonged effect may take place. Since the latter is uncomfortable to the patient, it is preferable to use the indwelling catheter.

Thrombosis of the internal carotid artery frequently occurs at or immediately distal to the bifurcation of the common carotid artery. Atheromatous plaques are most common in this region. That an atheromatous plaque may rupture and cause a dissecting hemorrhage resulting in occlusion was demonstrated on 1 patient. The external carotid artery could readily have been anastomosed to the distal portion of the internal carotid artery; however, from previous experience with ligation of the internal carotid artery for intracranial aneurysms it was thought that this was not justifiable, especially since in a few instances of persistent residues of a cerebrovascular accident, arteriograms do not demonstrate an obvious occlusion. Any cortical cell that has been subjected to complete anoxemia from 6 to 10 minutes appears to be permanently functionless. In other patients in whom complete hemiplegia occurs due to ischemia, reasonably normal function returns even though an occluded vessel may be demonstrated by arteriography. It seems wise, therefore, to increase the adequacy of the collateral circulation and at the same time to oxygenate the individual red cells as much as possible. Even though the administration of carbon dioxide appears to cause a dilatation of the cerebral vessels, this procedure does not seem physiologically efficacious to me when it is vitally necessary to increase the oxygen content of each red blood cell to effect as much oxygenation as possible to the still viable, though dormant, remaining brain tissue. The plan, therefore, should be to release the so-called associated vasospasm, increase the oxygenation of the red blood cells and also institute heparinization.

Thrombosis of the middle cerebral artery can be demonstrated by arteriography. However, these patients have not uniformly done well following interruption of the sympathetic nervous system either by injection of procaine or by removal of the superior and inferior cervical ganglions or the stellate ganglion. In general, the results of early interruption of the sympathetic nervous system may be of material help; late in the course of the disease—that is, after a few days or weeks—very little will be gained by the interruption of the sympathetic nerve. However, there have been several exceptions.

Interruption of the sympathetic superior cervical ganglion at the time of the ligation of the internal carotid artery—by the continuous flow of procaine, by actual excision of the ganglion or by division of the sympathetic trunk—has been of value in our experience.

So-called intermittent claudication of the brain as associated with Raynaud's disease or peripheral vascular disease—This is a vasospastic phenomenon and may occur intracranially, presumably resulting in convulsions, momentary loss of consciousness or temporary loss of vision in one or both eyes as a result of vasospasm of either the retinal arteries or the ophthalmic artery. A history of fatigue or unusual activity can usually be obtained from the patient as the initiating factor.

In 2 patients with moderately severe glaucoma as a complication of hypertension which had resulted in thrombosis of the central retinal vein, only a slight reduction in the intraocular pressure could be demonstrated several months after operation, even though immediately following surgery there had seemed to be material improvement. In 2 patients with retinitis pigmentosa, no material aid was noted so far as vision or change in the pigment was concerned. In these cases, several years have elapsed since the sympathetic nerve was interrupted and although the condition has not progressed greatly, it has not improved.

Exophthalmos—Bilateral interruption of the cervical sympathetic trunk, including removal of the superior cervical ganglion, was done in 7 patients with progressive exophthalmos following thyroidectomy. Recession of only 1 or 2 mm. of the eyeball could be noted immediately after operation. The operation was performed in the hope that the lowering of the upper eyelid and the narrowing of the palpebral fissure might help to protect the cornea. In none of the patients was this operation satisfactory.

In our experience, patients with atypical facial neuralgia are not helped by sympathectomy unless the neuralgia is of a true sympathetic nature. Since the diagnosis is difficult, a stellate block should be performed at the time the patient has the pain. If the pain is abolished promptly, a sympathectomy may be of help in those patients. We have had only 2 such patients who were completely and permanently relieved of their discomfort.

Migraine has not been alleviated by sympathectomy in our experience. Only 3 patients who were subjected to this procedure seemed to obtain relief from the stellate block; intensity, frequency and duration of attacks were not changed by the sympathectomy.

Facial paralysis—In partial facial paralysis associated with paralysis of the fifth nerve causing anesthesia of the cornea, lowering of the upper eyelid may be of material help in preventing recurrent ulcers.

Ménière's syndrome—Two patients were subjected to the removal of the stellate ganglion and ligation of the vertebral artery, seemingly with good results. Only 18 months have elapsed since the surgical intervention, so no conclusions can be reached except as to the immediate results. There are advantages, of course, to sympathectomy over division of the eighth nerve or removal of the labyrinth in that if the patient still has normal or reasonably normal hearing there will be no change in this particular factor. Also, the tinnitus is greatly reduced following the ligation of the vertebral artery and the removal of the stellate ganglion. However, unilateral Horner's syndrome which follows the removal of the stellate ganglion may be annoying to the patient.

Irritable carotid sinus—Many of these patients have incapacitating attacks of syncope. It is important that the proper diagnosis be made and all conservative measures—administration of belladonna derivatives, perhaps sympatholytic drugs and anticonvulsive drugs, and prevention of abnormal movements of the head—be instituted before sympathectomy is performed. In most instances the periarterial stripping with removal of the carotid sinus is of great help. I have not found it necessary to divide the cervical trunk or remove the stellate or superior cervical ganglions in these patients.

The scalenus anticus and/or cervical rib syndrome—Here again it is important to be certain of the diagnosis. I am skeptical about a purely isolated scalenus anticus syndrome. In most of these patients it is necessary to utilize myelography to be certain that there is no cervical intervertebral disk. I hesitate to operate on these patients without evidence of an abnormally elongated transverse process

or a cervical rib, or in the presence of a cervical rib. These patients seem to do much better by division of the anterior scalenus muscle and the removal of the cervical rib, with resection of the second and third thoracic sympathetic ganglions. This is especially true of patients who have considerable associated circulatory changes in the upper extremities.

The Extremities

Raynaud's disease—The results of sympathectomy in these patients have been disappointing especially as related to the index finger and color changes. We advise operation only when considerable trophic changes of the skin have taken place or when there is associated scleroderma.

Since time does not allow me to discuss the following clinical entities for which sympathectomy has been instituted, I shall mention them for the record: traumatic causalgias; reflex sympathetic dystrophy; arteritis; peripheral neuromas and nerve injuries; exploration of the brachial plexus; trophic ulcers; thromboangiitis obliterans; arteriosclerotic peripheral vascular disease; phantom limb pain; scleroderma.

Extremities, esophagus, lungs and heart—Aneurysms of peripheral arteries; fungous infection; recurrent phlebitis with vascular changes; trench foot; hyperhidrosis.

Thorax and Abdomen

Bronchial asthma; angina pectoris; aneurysm of abdominal aorta; postcholecystectomy colic; renal colic; Hirschsprung's disease; pancreatitis, chronic recurring; dysmenorrhea; hypertension.

I believe we all ought to accept the value of sympathectomy. In all instances, however, we should study the individual patient carefully before sympathectomy is instituted.

ANXIETY

ANXIETY is the reaction to danger. One cannot help suspecting, however, that the reason why the effect of anxiety occupies a unique position in the economy of the mind has something to do with the essential nature of danger. Yet danger is a universal human experience; dangers are the same for everybody. What we need and cannot lay our finger on is some factor which will explain why some people are able to subject the effect of anxiety, in spite of its unique quality, to the ordinary workings of the mind, or why others are doomed to break down over this task.

Sigmund Freud (1856-1939)

Physiologic Aspects of Anorexia Nervosa

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The voluntary starvation of anorexia nervosa offers an ideal means of studying the basic causes of edema. In an attempt to explain the edema of starvation, the authors performed fluid and electrolyte studies on a number of patients with anorexia nervosa. An illustrative case is presented in detail.

Although clinical and laboratory investigation of subjects who have starved voluntarily or as the result of famine or war has been extensive, knowledge of the formation of the associated edema has progressed slowly. While many physiologic accompaniments of edema are known, the basic causes for its development remain uncertain. In the voluntary starvation of anorexia nervosa one has available an ideal means of investigating this problem.

The original stimulus for investigative interest in edema occurred when Starling[1] published his concept of edema formation in 1896. As a result of his experiments he concluded that the osmotic pressure exerted by the circulating proteins was the most significant factor in the movement of fluid through the capillary wall. Little opportunity for practical investigation of his concept presented itself until World War I when severe undernutrition was prevalent throughout central and eastern Europe.

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In Germany it was observed that starvation often was accompanied by edema. The development of edema by only a portion of the individuals who displayed severe and approximately the same degrees of inanition aroused active controversy and speculation as to its cause.[2,3] Emphasis was placed on the importance of the serum proteins in maintaining dynamic equilibrium between the intravascular and interstitial fluids because observations of these substances were in keeping with Starling's theory of formation of edema. In reviewing the literature, it is found that the concentration of the serum proteins of about half the subjects examined was below the lower limit of normal. Further, values for serum proteins well within the limits of normal often were obtained and values which were definitely subnormal were not necessarily associated with edema.

During and following World War II, the lack of correlation between starvation edema

and the concentration of the serum proteins was noted.[4-6] From 1939 until 1942, starvation in the Warsaw Ghetto was extreme.[7] Inhabitants of this area were found to have either dry cachexia or "famine edema." During that period a total of 3,658 necropsies was performed and the records indicate that only 32.5 per cent of the victims were edematous. In 1942, approximately 500 laborers in the iron mines of the island of Elba were investigated.[8] As a result of a diet with a caloric value of 1500 and containing 78 gm. of protein, loss of weight varied between 10 kg. and 20 kg. Of this number of laborers, only 23 per cent exhibited edema. In 1945, Morgan, Wright and van Ravenswaay[9] examined 4,618 repatriated American prisoners of war from the Far East. Of this number, 465 (10 per cent) were edematous.

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In 1946, Keys and his associates[10] studied 34 men who subsisted on a European type of famine diet for six months. The diet provided an average of 49 gm. of protein daily and was similar to diets available in the less fortunate parts of western Europe early in 1945. The men lost an average of 24.5 per cent of their body weight. Pitting edema appeared within two months after the start of the famine diet in some instances and eventually affected all but a few of the group; even the few apparent exceptions were shown by special means to be waterlogged. There was marked increase in the voluntary intake of fluid with associated polyuria and nocturia; salt hunger was also pronounced.[11] In this study all of the subjects followed identical diets throughout the experiment.

Of those patients who have received a diagnosis of anorexia nervosa at the Mayo Clinic since 1917, less than 10 per cent have exhibited edema on admission. It has been difficult to understand why edema has not been observed with greater frequency, for the starvation of some patients had progressed to a degree which seemed almost incompatible with life. Information is lacking as to the exact amount of protein included in the diets of these patients before treatment. In a number of instances the caloric value of the daily diet has been roughly estimated to be between 900 and 1300;[12] these individuals drink exceedingly small amounts of fluid.[13] However, edema commonly occurs in the course of treatment.[14] In the more severe degrees of inanition, anasarca may occur with a concomitant gain in weight of about 15 pounds (6.8 kg.) within two weeks.

Previously, in the treatment of anorexia nervosa, patients were encouraged to eat a high protein diet, with a caloric value of approximately 3000. The results of this type of treatment were discouraging because of the postprandial sensations of epigastric fullness and abdominal distention which were invariably present, and vomiting or rumination without nausea which troubled a high percentage of patients immediately after eating. However, it was learned that small increases in the bulk of the diet could be made at regular intervals without causing the patient sufficient discomfort to be discouraging.

In 1938, a dietary regimen was devised[12,13] for the purpose of gradually increasing the "comfort capacity" of the stomach and decreasing the postprandial symptoms. This program consists of an initial high protein, high vitamin diet with a nutritive value of about 1300 calories. The diet is increased by weekly increments of 300 calories until the daily intake reaches 3200 calories. With this dietary regimen favorable results have been obtained within a comparatively short time.

In an attempt to explain the edema of starvation, fluid and electrolyte studies have been performed on a number of patients with anorexia

nervosa. Since the record of the following patient is typical, it will be presented in detail.

Presentation of Case

This patient first was seen at the Mayo Clinic in September 1948 (Figure 1a and b). At that time she was 34 years of age, 61½ inches (156.2 cm.) in height and weighed 58 pounds (26.3 kg.). She had subsisted, for the most part, on soups for several months and any attempt at eating solid foods led to vomiting. At the age of 20 years she had weighed 135 pounds (61.2 kg.). Three months following delivery, at the conclusion of an uneventful pregnancy in 1938, her weight had decreased to 90 pounds (40.8 kg.). Amenorrhea had been present since 1941. Axillary and pubic hair had been scanty for two years. Slight edema was present on examination; however, the degree of edema had been greater for the two preceding months. The basal metabolic rate was −30 per cent; the value for 17-ketosteroids* in the 24 hour specimen of urine was 1.4 mg. and for corticosteroids in the 24 hour specimen of urine, 0.42 mg. Results of routine laboratory examinations were not remarkable. Following a brief period of study the diagnosis of anorexia nervosa was made.

In April 1950, the patient returned for intensive study and treatment. In the interim she had limited her intake of food and water to prevent vomiting; despite this, for several weeks just prior to her return, vomiting had occurred following every meal. Edema had disappeared in 1948 and had not recurred. The patient's height had not changed, and she weighed 64.4 pounds (29.2 kg.), only slightly more than in 1948. Her weight was 51.1 per cent of the standard weight of 126 pounds (57.2 kg.). The systolic blood pressure was 76 mm. and the diastolic blood pressure was 44 mm. of mercury. The pulse rate was 59 per minute. The patient appeared to be emaciated and dehydrated; edema of the ankles could not be demonstrated. She was edentulous. With the exception of dryness of the skin and hair, which was scanty and short over the pubes and in the axillae, physical examination did not disclose anything remarkable.

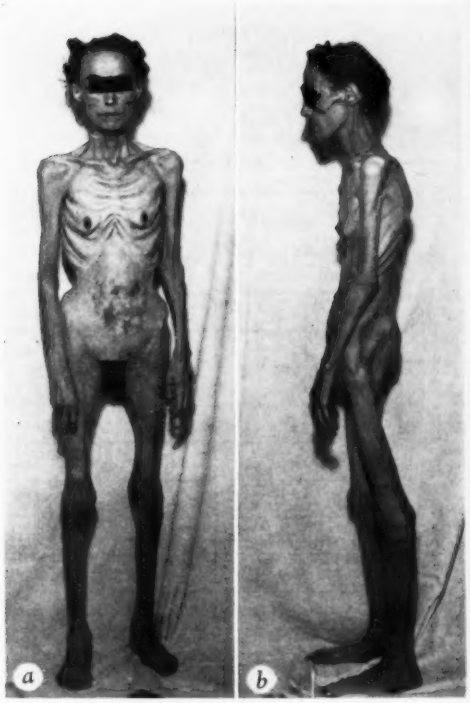

FIGURE 1. Appearance of patient, September 30, 1948; weight, 58 lbs. (26.3 kg.).

Investigations of renal function, including an excretory urogram, estimation of urea clearance and determination of the value for serum sulfate, all gave results within the limits of normal. Generalized osteoporosis was evident in the roentgenograms. The values for urinary steroids remained low: Those for 17-ketosteroids on April 10 and 12 and on May 3 were 0.6, 0.9 and 1.2 mg. per 24 hour specimen of urine respectively; comparable values for corticosteroids of 0.2, 0.28 and 0.58 per 24 hour specimen of urine were found. The basal metabolic rate varied from −12 to −23 per cent early in the study.

Procedure—The chloride balance study was begun the evening of April 8, 1950, and was terminated on June 18, 1950. The patient was maintained in a special metabolic unit in the hospital, where activity was kept approximately uniform from day to day. She was weighed at 7:30 A.M., before breakfast, and at 7:30 P.M. each day. Twelve hour collections of urine were terminated at these hours and each pooled; 12

*Values for corticosteroids and 17-ketosteroids were determined in the steroid laboratory under the direction of H. L. Mason. The method used for determining values for corticosteroids was essentially that of Corcoran and Page,[15] and for 17-ketosteroids by the method of Callow, Callow and Emmens,[16] with the addition of a correction equation to compensate for overestimation attributable to nonketonic chromogens.

TABLE 1

DIETARY SCHEDULE

DATE	DAILY CALORIC INTAKE	CARBOHYDRATE, GM.	FAT, GM.	PROTEIN, GM.	FOOD		ADDED NaCl., GM.	NONFOOD WATER INTAKE, ML.*
					Na., GM.	Cl., GM.		
April 9	1,412	108	87	50	0.57	0.91	1.3	1,280
10	1,401	124	79	49	0.57	0.90	2.0	1,220
11	1,120	90	64	45	0.59	0.90	2.0	1,025
12	1,444	116	84	59	0.67	1.11	2.0	1,220
13	1,568	126	91	61	0.70	1.14	2.0	1,300
14-17	1,359	141	60	64	0.48	0.69	5.0	1,800
18-21	1,631	164	67	67	0.98	1.34	5.0	1,800
22-25	1,909	211	85	77	1.10	1.32	5.0	2,300
26-28	2,213	248	92	99	1.11	2.07	5.0	2,300
29-May 7	2,213	248	92	99	1.11	2.07	8.0	2,300
May 8-12	2,533	293	107	101	1.19	1.51	8.0	2,300
13-29	3,255	359	151	114	1.41	2.29	8.0	2,300
30-June 7	2,200	253	94	85	0.61	1.02	0	2,300
June 8-14	2,200	253	94	85	0.61	1.02	8.0	2,300
15 on	3,255	359	151	114	1.41	2.29	8.0	2,300

*See Table 3 for total intake of fluid.

hour collection was examined for volume, specific gravity and the amount of chloride* present. All stools were weighed and the amount of chloride present determined. Resting blood pressure was determined twice daily.

During the first five days the patient was asked to eat all the food served her; however, the type and quantity of the foods, as well as the amount of fluid served, had been determined previously in accordance with the preference of the patient.† Thereafter, a rigid dietary schedule was followed, as is outlined in Table 1. The entire amount of food, salt and water allotted for the day was consumed throughout the study and at no time did vomiting occur.

All food was weighed. All vegetables, fruits, bread and butter used were salt-free. Distilled water and dialyzed milk were used. Because the subject was edentulous and had not been supplied with dentures, all meats and solid foods were ground. Electrolyte data are based on actual chemical‡ analyses of the food.

Other than reassurance and dietary management, the only treatment consisted of administration of phenobarbital, ½ gr. (0.032 gm.) three times daily, 10 drops of tincture of belladonna in water before meals and injections of cortisone over a period of 10 days, from May 19 to May 28, inclusive. Cortisone, 100 mg., was administered the first day and 50 mg. each day thereafter. The only obvious effect of the cortisone was to elevate the values for urinary steroids during the brief period of treatment (maximal values: 1.6 mg. 17-ketosteroids and 1.98

*The amounts of chloride in the urine and stool were determined for fluid balance studies by a special technician under the supervision of Belding H. Scribner. The method used was Scribner's modification[17] of the mercurimetric determination of chloride described by Dubsky and Trtílek.[18]

†During this period the caloric value of the daily diets varied from 1,020 to 1,581. Diets of these caloric values would not permit maintenance of weight of a normal adult.

‡Accepted standard chemical procedures routinely employed at the Mayo Clinic were used in determining amounts of substances in the blood and plasma, as well as in analyses of samples of the various diets served. Determinations were made in the research chemical laboratory under the direction of Marschelle H. Power.

mg. corticosteroids per 24 hour specimen of urine).

Repeated determinations of sodium, chloride and carbon dioxide of the serum were within the limits of normal throughout this study (Table 2). In the absence of any disturbance in acid-base balance, we assume that the data relative to chloride are comparable to those relative to sodium and we therefore use chloride values rather than the more significant sodium values, the chemical determinations of which are more difficult.

Results—The interrelationships of diet, weight, edema, intake of chloride and excretion of chloride are seen in Figure 2 for the entire period of investigation. The difference between

TABLE 2, PART 1

LABORATORY DATA: HEMODILUTION APPEARED WHEN EDEMA DEVELOPED AND HEMOCONCENTRATION AS EDEMA DISAPPEARED

DATE	HEMATOCRIT, PER CENT RBC	HEMOGLOBIN, GM. PER 100 CC.	ERYTHROCYTES, MILLIONS PER CU. MM.	SERUM PROTEINS	
				OBSERVED, GM. PER 100 CC.	CALCULATED*, GM. PER 100 CC.
April 10		11.7	4.02	5.4	5.4
11	40				
12	43	13.4	4.09	5.3	4.9
17	41	11.5	3.91	4.8	4.7
20	38	11.4	3.66	5.1	5.4
24	38	10.8	3.61	4.9	5.2
27	38	11.4	3.20	5.4	5.7
28	36				
May 1	39	11.4	3.93	5.3	5.4
4	37	11.0	3.58	5.2	5.6
8	36	11.0	3.11	5.4	6.0
9	37				
11	38	10.9	3.53	5.3	5.6
15	38	10.9	3.63	5.3	5.6
18	36	10.8	3.52	5.6	6.2
19	36				
20			3.66		
22	35	10.2	3.03	5.4	6.2
25	34	10.3	3.40	5.3	6.3
29	35	10.0	3.08	5.6	6.4
30	34				
June 1	36	10.6	4.20	5.9	6.5
5	36	11.0	3.94	6.0	6.7
8	38	11.9	4.20	6.3	6.6
12	38	12.0	3.80	6.3	6.6
15	34	10.8	3.45	5.5	6.5
19	36	10.6	3.73	5.6	6.2
22	34	10.6	3.92	5.9	6.9

*Serum proteins corrected for hemodilution; e.g., on June 1, the hematocrit value is 36 per cent compared with 40 per cent originally, the observed serum protein level is 5.9 gm. per 100 cc.; therefore, $\frac{40}{36} \times 5.9 = 6.5$ gm. per 100 cc.

TABLE 2, PART 2

LABORATORY DATA: NORMAL VALUES FOR SODIUM, CHLORIDE AND CARBON DIOXIDE IN THE SERUM INDICATED; NO ALTERATION OF ACID-BASE BALANCE

DATE	SERUM CHLORIDE, MEQ. PER LITER	SERUM SODIUM, MEQ. PER LITER	CARBON DIOXIDE, MEQ. PER LITER	BLOOD VOLUME, ML.[10]	PLASMA VOLUME, ML.	RED CELL VOLUME,* ML.	EDEMA†
April 10	106	135	29.5				0
11				2,750	1,650	1,110	0
12	102		31				0
17	102		32.5				+
20	103		32				+
24	104	143	32				++
27	104		31				+++
28				3,106	1,988	1,118	+++
May 1	103		33				+++
4	105	142	31				++++
8	104		31				++++
9				3,286	2,070	1,216	++++
11	104		33				++++
15	103		33				++++
18	103	139	32				++++
19				3,484	2,230	1,254	++++
20							++++
22	104		32				++++
25	103		29				++++
29	103						++++
30				3,491	2,304	1,187	++++
June 1	103		32				+++
5	100		33				+
8	100	143	33	3,147	1,951	1,196	0
12	104		31				+
15	105		29				++
19	107		30				++
22	104			3,406	2,248	1,158	++

*Calculated by difference between whole blood volume and plasma volume.
†Edema judged on arbitrary scale: 0 = none, ++++ = maximal edema.

the two weight curves, which represents approximately 3 pounds (1.4 kg.), reflects the high daytime intake of fluid with low urinary excretion and the high nighttime urinary excretion.

The weight is seen to have risen steadily as the caloric value of the diet was increased and to have fallen when the caloric value of the diet was decreased from 3200 calories to 2200 calories. However, later, on June 9, the weight curve abruptly rose, without a parallel increase in the caloric value of the diet.

Figure 2 further shows that the gain in weight and the development of edema were only incidentally related to the caloric value of the diet. When the daily intake of chloride was reduced, on May 30, to 28 mEq. the weight

dropped sharply and edema disappeared. Subsequently the dietary chloride was increased by the addition of 8 gm. of sodium chloride. A gain in weight occurred promptly and edema recurred.

The changing appearance of the patient from April to June 1950 is represented in Figure 3.

The marked retention of chloride is demonstrated when the values for chloride are plotted on a cumulative basis (Figure 4). Assuming a chloride concentration of approximately 100 mEq. per liter of extracellular fluid, one would anticipate the retention of about 1 liter of water with each 100 mEq. of chloride retained. As

TABLE 3

REPRESENTATIVE DATA ON FLUID INTAKE AND OUTPUT

During the first period water and chloride were retained in significant amounts; this was reversed during the first week of June when the intake of chloride was limited to 28 mEq. daily.

DATE	TOTAL FLUID INTAKE, ML.*	URINE					
		7:30 A.M. to 7:30 P.M.			7:30 P.M. to 7:30 A.M.		
		volume, ml.	sp. gr.	*p*H	volume, ml.	sp. gr.	*p*H
April 9	2,120	85	1.025	6.0	41	1.020	6.0
10	2,045	83	1.030	6.0	125	1.024	5.8
11	1,525	100	1.024	6.0	245	1.010	5.5
12	2,035	160	1.022	5.5	500	1.010	5.5
13	2,110	118	1.025	5.8	238	1.012	5.5
14	2,400	327	1.012	5.5	850	1.006	5.0
15	2,400	560		5.5	925	1.006	5.5
16	2,400	325	1.014	6.0	920	1.005	6.0
22	3,050	640	1.011	5.8	1,040	1.010	6.0
26	3,200	600	1.008	6.0	1,160	1.006	6.0
May 9	3,250	720	1.010	6.0	1,220	1.005	6.0
13	3,300	680	1.014	6.0	1,300	1.007	6.0
29	3,300	780	1.012	6.0	1,430	1.010	6.5
30	2,850	1,780	1.010	6.0	1,380	1.010	6.0
31	2,850	1,470	1.006	5.8	1,180	1.012	5.8
June 1	2,850	1,090	1.005	6.0	1,120	1.009	6.0
2	2,850	1,350	1.002	6.0	1,015	1.007	6.0
3	2,850	1,120	1.010	5.5	1,200	1.008	
4	2,850	1,240	1.004	5.5	1,005	1.006	5.5
5	2,850	1,110	1.006	5.5	980	1.006	5.5
6	2,850	1,250	1.004	5.5	1,060	1.007	5.5
7	2,850	1,100	1.005	5.5	1,080	1.010	
8	2,850	760	1.009	5.5	780	1.007	
9	2,850	850	1.005	5.5	920	1.005	
10	2,850	1,040	1.004	5.5	880	1.010	
11	2,850	760	1.008	5.5	1,240	1.010	6.0
12	2,850	620	1.007	5.5	910	1.007	
13	2,850	1,020	1.010	5.5	960	1.010	

*Fluid intake limited to the daytime hours except on June 10 and June 11, when 200 ml. were taken after 7:30 P.M.

seen in Figure 4, however, the retention of chloride was far greater than the gain in weight and therefore than the amount of water retained.

When the retained chloride had accumulated to 3000 mEq., instead of the expected water retention of 30 liters (30 kg.) the total gain in weight was only 11 kg. It may be seen further that the retention of chloride exceeded that of water (weight gain) throughout the study except for the brief period of weight loss associated with loss of edema (Figure 2). It is difficult to believe that technical errors alone could account for this remarkable discrepancy between chloride and water.

When data on fluid balance are inspected closely another interesting phenomenon is apparent (Table 3). During the twelve hours of daytime (7:30 A.M. to 7:30 P.M.) the volume of urine was considerably lower than it was in the succeeding 12 hours of nighttime. The excess of night volume of urine over day volume persisted throughout the study, with the exception of the period during the first week in June when there was rapid loss of weight. As the intake of fluid increased, the only apparent change was reduction in the specific gravity of the urine. Reduced urinary excretion in daytime often is encountered among patients with severe hypotension, apparently because of reduced hydrostatic pressure in the renal arteriolar tree when the patient is erect; in the case reported here, the importance of the hypotension in relation to the lagging urinary excretion is not known.

Any increase in the extracellular space sufficient to produce edema such as this patient exhibited should be associated with comparable hemodilution. That this did occur is demonstrated in Table 2. In the determinations of blood volume,* it was noted that the total volume of red cells in the body remained practically stationary throughout the study but that the plasma volume, and therefore the whole blood volume, tended to increase or decrease as edema appeared or disappeared. Hematocrit, hemoglobin and erythrocyte values likewise demonstrated the hemodilution phenomenon, while values for serum sodium and serum chloride remained nearly unchanged. The influence of this cyclic hemodilution on the values for serum protein is not demonstrated so clearly, for when the actually observed values for serum protein are corrected for hemodilution, using the hematocrit value as a standard, there is seen to be a slow, rather steady rise. The initial observed value for serum proteins was 5.4 gm. per 100 cc. in the absence of edema but this value increased to 6.3 gm. in the only other period (June 8) during which pitting edema could not be demonstrated. Despite this difference in the values for serum proteins, demonstrable edema appeared in each instance when retention of chloride began. Even though the initial value for serum proteins (5.4 gm.) was near the so-called edema level, edema was not demonstrable and did not become evident until approximately 500 mEq. of chloride had been retained. It should be noted, however, that

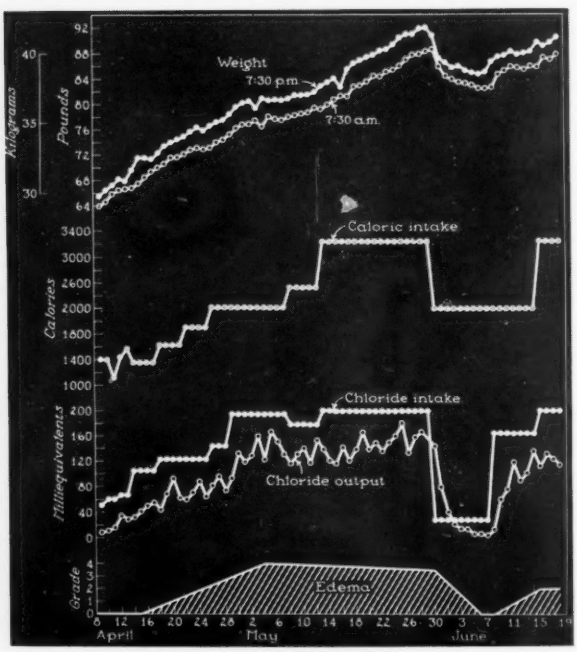

FIGURE 2. Interrelationship of diet, weight, edema, intake of chloride and excretion of chloride.

*Volumes of blood and plasma were determined by the method (Congo Red) described by Rowntree, Brown and Roth.[19]

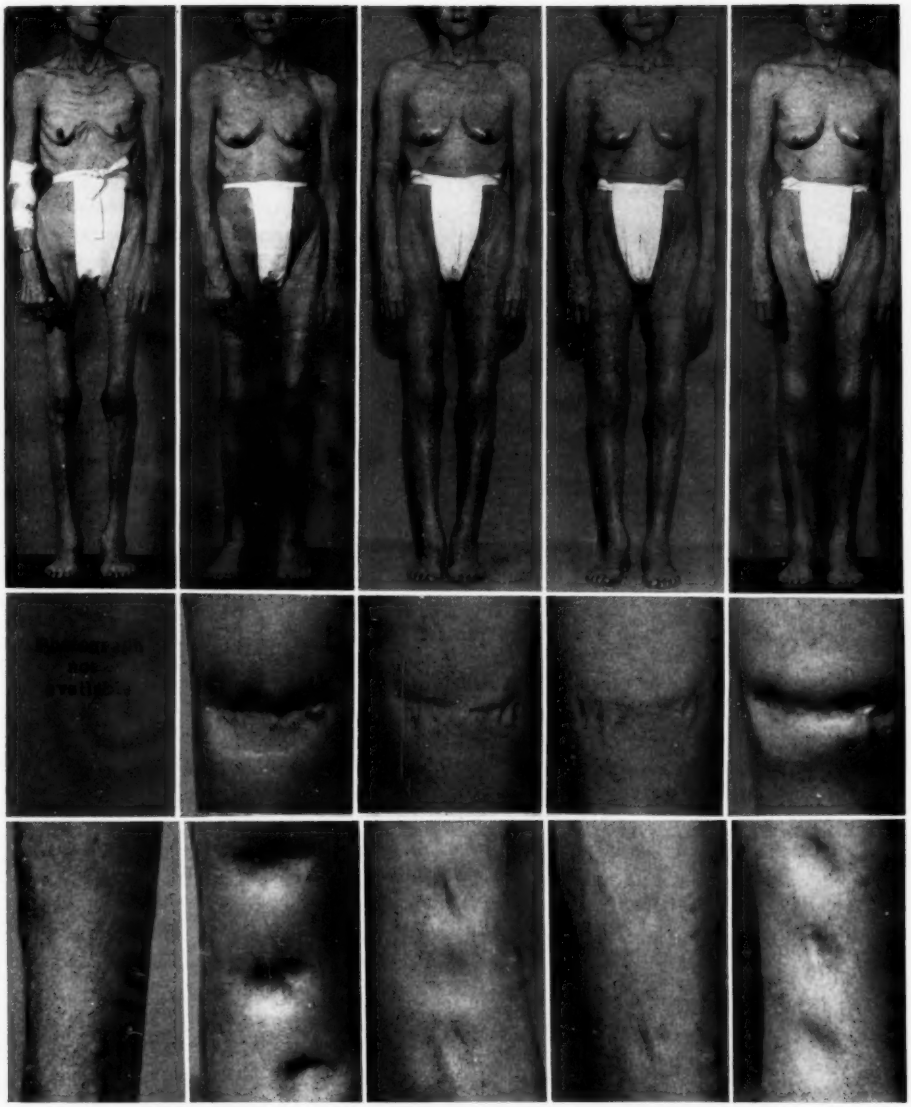

FIGURE 3. From above downward: (1) appearance of patient, (2) denting of calf of leg from its having rested for a few moments on edge of chair and (3) presence or absence of pitting edema of ankle.

with comparable amounts of chloride retained, edema was present to a greater degree when the values for serum proteins were particularly low.

Colloid osmotic pressures of the blood calculated from the values for serum proteins are listed in Table 4. By the methods of either Keys[20] or of Govaerts,[21] the first colloid osmotic pressure was depressed to "edema levels" but, as mentioned previously, edema was absent and was not demonstrable until the value for serum proteins had been further decreased as a result of dilution. When edema reappeared in

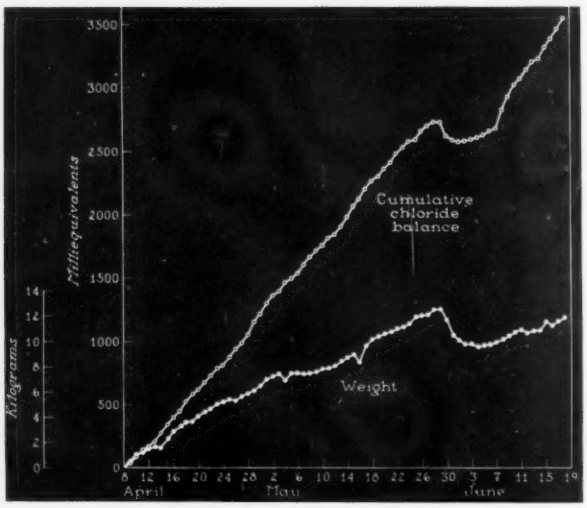

FIGURE 4. Retention of chloride plotted on a cumulative basis in relation to gain in weight of patient.

June the colloid osmotic pressure, as calculated by both methods, was above "edema levels."

The steady improvement in the condition of the patient during most of the study period of 76 days is indicated in the serial photographs (Figure 3). In addition to physical improvement, her mental outlook brightened. The marked hypotension present at the time of admission gradually diminished until the blood pressures were systolic 110 mm. and diastolic 70 mm. of mercury. Correspondence with the patient one and three months later indicated that her further progress had been satisfactory. Edema had disappeared, returning only briefly a time or two. Her appetite had not diminished and her weight had remained at about 90 pounds (40.8 kg.).

Comment

The successful completion of circulation between the capillary and the extracellular space is dependent on a balance between the intravascular and extravascular hydrostatic pressures on the one hand and the intravascular and extravascular colloid osmotic pressures on the other. With this concept, Starling postulated that imbalance affecting any one of these four factors, leading to the outward flow of fluid through the capillary wall, was responsible for edema. Many examples of such imbalance amply confirm Starling's hypothesis; for example, reduction of the value for plasma proteins in experiments on plasmapheresis leads to the development of edema;[22] or doubling the venous pressure leads to the development of edema by raising the intracapillary hydrostatic pressure.[23]

None of these four pressure factors is obviously defective in the presence of the edema which is observed at times in association with involuntary (famine) or voluntary (anorexia nervosa) starvation, or in the presence of the edema which develops as a result of forced feeding in the treatment of anorexia nervosa. In the presence of these circumstances, the following should be kept in mind: (1) The colloid osmotic pressure of edema fluid is believed to be low; (2) the venous pressures and, thereby, probably the capillary pressures, are low; (3) it is doubtful whether reduction of tissue pressures from their already low levels to zero could significantly cause, or increase the degree of, edema; (4) by exclusion, reduction of the colloid osmotic pressure of the plasma has been most frequently suspected of causing the formation of edema. However, careful analysis of the data of Keys and associates[11] cannot confirm that the lowered osmotic pressure is sufficient to produce edema. Similarly, in the case herein reported, despite a lowered value for serum protein (5.4 gm.), edema was not evident until the intake of food and salt was increased, and edema did occur subsequently when the value for serum protein approached normal.

It therefore seems that Starling's hypothesis of formation of edema may be incomplete. Some have suggested that in starvation the kidney is unable to secrete chloride normally;[24] others, that there is an increased affinity of the tissues for the chloride ion.[25] While either mechanism possibly could explain formation of edema, no positive evidence has been put forward which has found wide acceptance.

These fundamental facts remain: Ingestion by a patient with anorexia nervosa of small amounts of sodium chloride was accompanied by the development of edema; retention of chloride continued as long as sodium chloride

was served the subject in any appreciable amount; despite the prolonged positive balance, excretion of chloride in the urine almost disappeared when the chloride in the diet was sharply reduced; retention of chloride far outdistanced retention of water, which leads to the unanswered question as to the disposition of the excess chloride. If the chloride is retained in the extracellular space, the interstitial fluid must be hypertonic with respect to the blood; the alternative is an intracellular disposition of the chloride. The available data are insufficient to allow one to judge between increased avidity of the tissues for chloride on the one hand and inadequate renal clearance of electrolyte on the other.

Attention to the chloride problem may explain the development of edema only sporadically among individuals who are undergoing starvation. The initial weight of the subject of the present study indicates a previous diet of low caloric value. The original high urinary specific gravity, with small volume of urine and low concentration of urinary chloride, are evidence of limited intake of fluid and negligible consumption of sodium chloride; the subject was not edematous. On the other hand, of the 32 voluntary starvers studied by Keys and his associates,[11] all but 4 became edematous. The daily intake of sodium chloride of these men was 9 to 14 gm. and they might, therefore, be comparable to patients with anorexia nervosa when the intake of sodium chloride of such patients is increased and they likewise become

TABLE 4

COLLOID OSMOTIC PRESSURES OF SERUM PROTEINS

DATE	EDEMA*	SERUM PROTEIN			COLLOID OSMOTIC PRESSURE	
		Albumin	Globulin	Total	Keys[20]	Govaerts[21]
April 10	0	3.7	1.7	5.4	223	312
12	0	3.6	1.7	5.3	217	305
17	+	3.3	1.5	4.8	191	278
20	+	3.3	1.8	5.1	201	284
24	++	3.6	1.3	4.9	203	297
27	+++	3.6	1.8	5.4	220	307
May 1	+++	3.6	1.7	5.3	217	305
4	++++	3.4	1.8	5.2	207	292
8	++++	3.9	1.5	5.4	229	323
11	++++	3.7	1.6	5.3	220	310
15	++++	3.6	1.7	5.3	217	305
18	++++	3.8	1.8	5.6	234	322
22	++++	3.8	1.6	5.4	226	318
25	++++	3.6	1.7	5.3	217	305
29	++++	3.8	1.8	5.6	234	322
June 1	+++	4.0	1.9	5.9	252	339
5	+	3.8	2.2	6.0	248	330
8	0	4.2	2.1	6.3	276	358
12	+	4.1	2.2	6.3	272	352
15	++	3.9	1.6	5.5	233	325
19	++	3.9	1.7	5.6	237	327
22	++	4.0	1.9	5.9	252	339

*Arbitrary scale: 0 (none) to ++++ (severe edema).

edematous. The usual patient with anorexia nervosa voluntarily limits the intake of food, fluid and salt and remains free of edema.

Summary

In a case of severe anorexia nervosa, despite a reduced value for serum proteins, edema was not demonstrable until a week after the institution of a vigorous feeding program. Edema fluctuated, thereafter, with relation to the intake of sodium chloride. During the 76 days of the study, the net retention of chloride of the subject was in excess of 3000 mEq.; the retention of fluid, based on the gain in weight, was only about 10 liters and not the expected 25 plus liters.

Starling's hypothesis of formation of edema does not seem sufficient to explain the edema which develops in cases of anorexia nervosa. Furthermore, from observations of "starvation edema" as it occurs in association with this condition, it would seem that the edema is related to a disturbance in metabolism of sodium chloride. The fundamental nature of the deranged metabolism is not known.

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MEETINGS AND POSTGRADUATE COURSES

University of Kansas Medical Center, Kansas City Postgraduate course in gastroenterology, December 8-11. For details, write: Extension Program in Medicine, University of Kansas Medical Center, Kansas City 12, Kansas.

Eighth International Congress of Rheumatic Diseases to be held at Geneva, Switzerland, and Aix-les-Bains, France, August 24-28, 1953. For details, write to Professor K. M. Walthard, Institut de Physiatrie, Hôpital Cantonal, Geneva, Switzerland.

University of Minnesota Medical School, Minneapolis: Continuation course in gynecology, for specialists, December 15-17, at the Center for Continuation Study. Visiting faculty member will be Dr. Arthur Hertig of Harvard Medical School; director of the course will be Dr. John L. McKelvey.

Continuation course in anesthesiology for general physicians, January 8-10, at the Center for Continuation Study. Visiting faculty members will be Dr. Donald E. Hale, Cleveland; Dr. Sidney O. Orth, Madison, and Dr. Daniel C. Moore, Seattle. Director of the course will be Dr. Ralph T. Knight.

Trigeminal Neuralgia and Mandibular Joint Dysfunction

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Trigeminal neuralgia is a symptom complex consisting of paroxysmal attacks of pain manifesting itself in one or more branches of the trigeminal nerve. Mandibular joint dysfunction in many instances may be an etiologic factor. A reconsideration of the entire trigeminal area and its relation to masticatory apparatus is mandatory, as the anatomy of the attachment of the mandible to the skull provides very obvious chances for impingement of the condyle on sensory nerve branches. The basis of this report involves correction of the temporomandibular joint dysfunction and rehabilitation of these patients by the proper dental occlusion.

TRIGEMINAL neuralgia is characterized by a paroxysmal attack of pain involving one or more branches of the trigeminal nerve. The cause of the affliction is unknown. This, in substance, is the usual definition given and accepted in the literature.

Since Fothergill's classic description in 1773, "On the Subject of a Painful Affection of the Face," very little has been added to the description of the affliction. It must be emphasized that trigeminal neuralgia is a symptom complex, completely subjective and descriptive. The term "neuralgia" is used to describe a sharp, paroxysmal pain, excruciating in nature, along the course of a sensory nerve, the etiology of which is unknown. It is not a disease. Hence, by definition "neuralgia" is an implicit assertion that no cause of the pain is known.

Descriptive terminology in the past has gone to great lengths to differentiate trigeminal neuralgia into so-called major and minor neuralgias. The former is characterized by a sharp, lancinating, piercing pain which has been described as unbearable, radiating from one portion of the face to another, occurring in paroxysms, hence called "tic douloureux."

The minor neuralgia or atypical neuralgia has been described as possessing the quality of pain which is deep and constant, unassociated with dolorogenic or "trigger" zones. The basic point, however, remains that the pain is mediated along the course of the trigeminal nerve and the effective output must depend to a great extent on the intensity and duration of the unknown stimulus.

It is interesting that way back in 1773 Fothergill in describing this situation pointed out (1) that this pain occurs most often in people over 40 years of age; (2) that it seems to occur more often in women; (3) that many of these patients are edentulous, and (4) that the pain is initiated by chewing, sneezing and

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coughing—i.e., by some movement of the mandibular mechanism.

It will be noted that this disease is predominantly a disease of the fifth, sixth and seventh decades of life—that it seems to be a disease complex of advanced age. It is not uncommon. Dogliotti of Italy reported over 2000 cases. Peet in 1932 reported a collected series of Adson, Frazier and his own consisting of over 2000 cases. Recently, Grant reported 1400 such cases. Harris of England accumulated 1500 patients. It seems reasonable to assume that this order of magnitude will be found in many well established neurologic centers.

Heretofore the therapy has been historic. The patient has a pain in the face and the sensory nerve is interrupted. In culling the literature one comes across such diverse therapies as the following: "It is advised that the steaming hot entrails of a freshly killed pigeon be thrown in the face of the sufferer." It was about the time of Bell that the English advised the sufferer to take over that new game coming across from America, namely, poker, because the patient would keep a poker face and thus not set up the pain reflex. In other words, the therapy heretofore has been diverse, varying in extent, but primarily based on the thesis that the sensory nerve mediation must be interrupted either chemically or surgically, the latter constituting one of the most brilliant chapters in neurologic surgery.

However, it is a procedure of expediency. The patient comes into the office. One listens to his complaint. He describes a sharp, excruciating, lancinating pain. One nods and states, "Ah! Trigeminal neuralgia, tic douloureux." He is sent into the hospital and frequently the operation assumes the proportion of an emergency procedure demanded by the patient. Not infrequently, the function of the dentist has been to appear more or less as the culprit. In the initial phases of pain, teeth have been extracted, usually in the general area where the pain seemed to originate.

It is our opinion that a reconsideration of the entire trigeminal area and its relation to masticatory apparatus is mandatory. In this situation the dentist no longer appears in a negative role but assumes the stature of an ancillary specialist in medicine. In general, there has been little regard for the examination or consideration of the occlusion of natural teeth, and, more so, of artificial dentures. The emphasis on occlusion and function of the temporomandibular joint as one unit of the masticatory apparatus is of paramount importance.

We were impressed by Costen's description of a so-called temporomandibular joint symptom complex characterized by pain in the temporomandibular joint and frequently associated with pain along the tongue and mandible. His explanation of this pain is that the malocclusion of the teeth produces a shift of the condylar mechanism, and the condyle or its capsular components and the diseased tissues associated with this shifting produce tension on the chorda tympani and on branches of the auriculotemporal nerve which innervates the capsular area. Some students feel that the chorda tympani could not be thus impinged on, and also that from anatomic and neurophysiologic evidence the chorda tympani does not carry pain fibers. In a rather extraordinary opportunity, Drs. Costen, Clare and Bishop were able to visualize the chorda tympani nerve in a patient who had had a mastoidectomy in which the drum was absent. With a camel hair electrode they were able to stimulate the chorda tympani nerve and produce pain along the anterior two-thirds of the tongue, thus demonstrating that the chorda tympani does carry pain.

The proof of the pudding, in our opinion, was that these patients did get better when

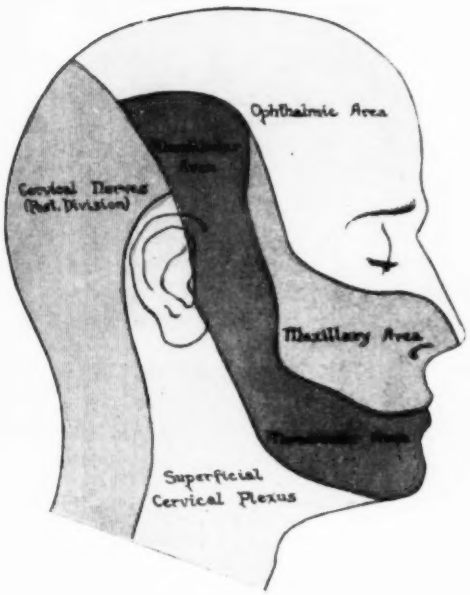


FIGURE 1. Conventional distribution of the trigeminal divisions—ophthalmic, maxillary and mandibular.

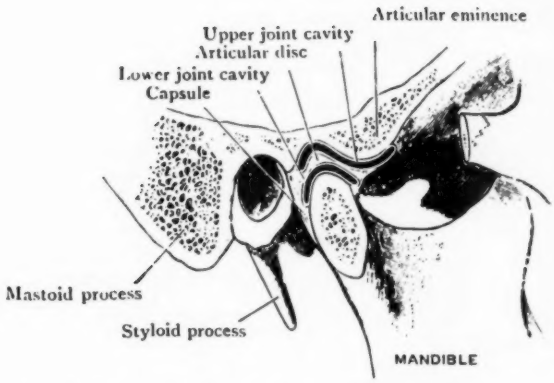


FIGURE 2. A cross section of the temporomandibular joint discloses that it is a rather complicated joint. It moves not only up and down but also forward and backward and medially and laterally; it has a space above, a space below, a capsule between, ligaments around it, muscles, nerve tissue and blood vessels.

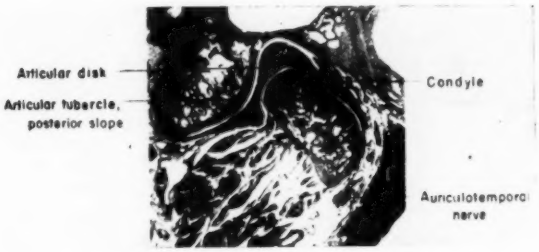


FIGURE 3. A slide from Dr. S. W. Chase of Western Reserve University showing the intrinsic anatomy; this illustrates the auriculotemporal nerve and its definite juxtaposition to the condyle so it can be impinged upon.

their bite mechanism was altered. The thought occurred to us, therefore, that if we altered the bite in patients suffering from trigeminal neuralgia we might save these patients from operation, which in some instances does produce unfortunate results such as paresthesia, corneal disturbances and, sometimes, peripheral seventh nerve palsies. It was with this thought in mind that we examined such patients with a view to altering their bite. This seemed like hauling coals to Newcastle. Many of these patients in the past had had their teeth extracted, and the dentist appeared as a culprit, as a villain; he took out the teeth in the pain area, when actually the idea is to put teeth back in and alter this situation.

Correction of the temporomandibular joint dysfunction will give relief in many instances. Should failure or expediency dictate, various well established neurosurgical procedures can then be instituted. Such a course of conservatism enables the patient to obtain relief without loss of sensory or, possibly, motor function.

If repositioning fails (and we have had failures), one can always perform surgery. For patients who cannot undergo this procedure because of distance, accessibility, etc., one can interrupt the nerve pathway purely as a matter of expediency, but certainly we think this conservative attitude and re-evaluation of the whole masticatory apparatus with a view to altering the bite position warrants investigation.

Following this line of reasoning, we have had occasion to observe 54 patients within the past three years, all of whom were sent

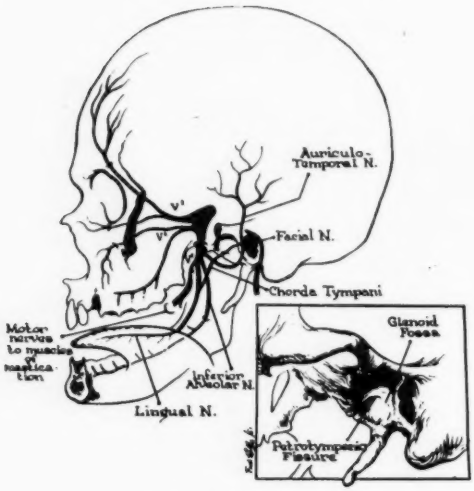
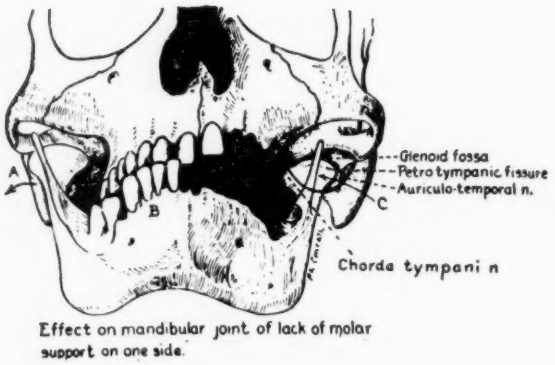


FIGURE 4. A slide of Dr. J. B. Costen, showing the relationship of the chorda tympani nerve, a branch of the seventh. It carries pain fibers and has connections with the lingual nerve, a branch of the mandibular. Recent work has shown that the auriculotemporal nerve issues from the petrotympanic fissure in the glenoid fossa and that it is conceivable that it can be impinged upon or irritated by adjacent tissues which are affected with a pathologic process. That is Costen's thesis.



Effect on mandibular joint of lack of molar support on one side.

FIGURE 5. Malocclusion and loss of tooth support. Many of these patients have edentulous areas and it is expected that a form of malocclusion is a contributing factor in production of pain. The loss of teeth per se is not indicative of this situation, but frequently edentulous people do have malocclusion of this type and thus the result. Instead of the upper teeth being over the lower, the lower are above the upper, the jaw is shifted and there is impingement upon the nerve components as already mentioned.

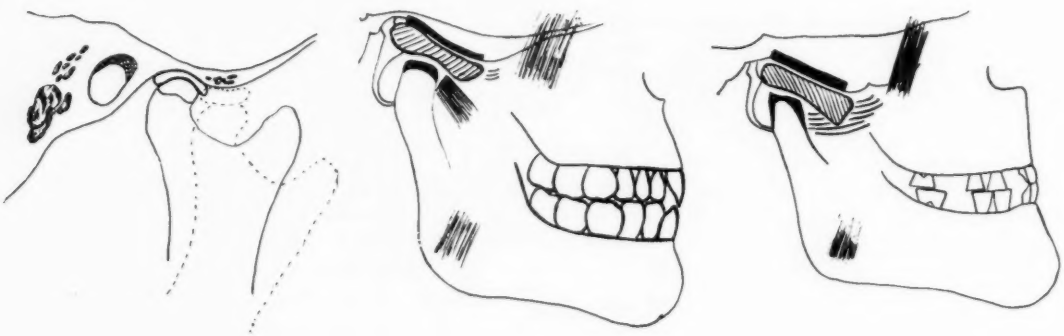


FIGURE 6 *(left)*. The temporomandibular joint in normal rest position is indicated by the continuous line. The dotted outline of the joint indicates the condition when the mandible is depressed. Note the condyle coming out of the glenoid cavity and the articular disk falling forward.

FIGURE 7 *(center)*. Modified drawing from G. Steinhardt, illustrating a normal joint with good occlusion, namely, an overbite in the anterior area with a continuous curve going backward and downward to the first molar and then upward to a continuous slope anteriorly to the anterior aspect of the glenoid cavity and condyle.

FIGURE 8 *(right)*. Modified drawing from G. Steinhardt. In cases of malocclusion there is a type of flat occlusion, namely, a loss of curve due to worn, abraded teeth or missing teeth. Visualizing this upward sweep in a continuous cycle, the condyle is almost symmetric with the plane of occlusion and teeth.

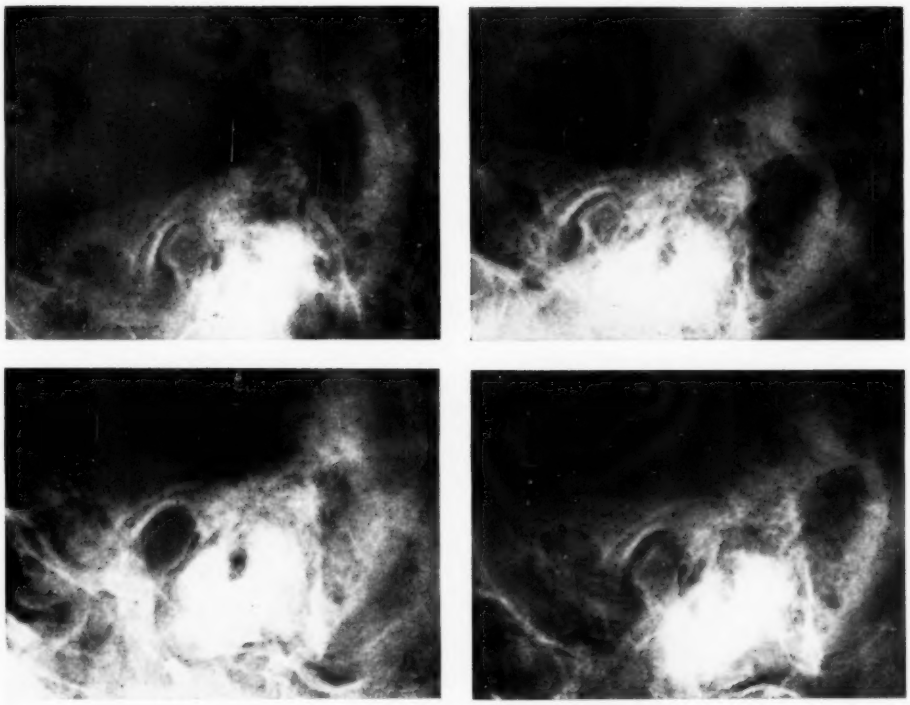


FIGURE 9 *(top, left)*. Radiogram taken in a closed position indicates a shallowing of the glenoid cavity and a sharpening of the eminence resulting in a posterior-superior displacement.

FIGURE 10 *(top, right)*. The same joint after dentures had been worn for four months. Where there formerly was contact or a superior-posterior displacement of the condyle within the cavity, there is now a slight spacing which indicates that the new dentures with balanced occlusion have repositioned the condyle.

FIGURE 11 *(bottom, left)*. Temporomandibular radiogram of the condyle of the same patient. The condyle glides out of the glenoid cavity and forward to the eminence.

FIGURE 12 *(bottom, right)*. Radiogram taken in the open position of the same condyle after treatment. Note that the condyle is restricted within the glenoid cavity. It does not move forward or out of position. The condyle is restricted in effect by the balance of the occlusion of the mouth brought about by the new dentures.

to us with a diagnosis of trigeminal neuralgia. In this group there have been some, paradoxically, sent to us by dentists. By careful elicitation of the history, examination of the dental state, together with proper conservative construction of the mechanics of the temporomandibular joint, relief has been effected in 15 cases of major neuralgia with 4 failures and in 21 cases of minor neuralgia with 7 failures. Three patients who had had posterior rhizotomy did not respond. Seven others still have occasional episodes of discomfort.

In general the following program is instituted in the rehabilitation of such patients:

1. Many of these patients are in a state of acute distress and great emotional tension which may be associated with the clinical picture. They are given sedatives in the form of mild barbiturates plus codeine or, if necessary, are hospitalized.

FIGURE 13. This illustration shows the patient pointing to the area of pain. This pain was very sharp, excruciating and lancinating. There was also pain in the tongue.

2. A detailed medical history and record of environmental background are obtained, together with a description of subjective symptoms and discomfort.

3. Complete radiograms are made of the entire mouth and of the dental structure and temporomandibular joint, and study models of natural dentition or of artificial dentures are obtained. In patients with dentures a complete history of denture experience is elicited, with careful scrutiny as to the condition, quality, etc., of the set worn. Also, intraoral and extraoral photographs are taken of the patient's occlusion, bite and centric and vertical dimensions.

4. The models of the patient's teeth are mounted and studied.

5. Dental radiograms are interpreted but extractions are deferred temporarily (unless

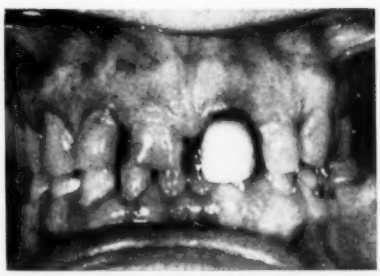


FIGURE 14. Dental examination revealed occlusion of the teeth and a number of missing teeth on the lower and upper right side. We are interested in dental infections as evidenced here by the right central. We defer oral surgery and extractions; at this time, such treatment would only add insult to injury—the patient is interested in relief of the severe pain.

FIGURE 15. After proper correlation between temporomandibular radiograms and study models, and examination of malocclusion, this case was planned as follows: silver splints attached or fixed to the lower posterior teeth on the right and likewise on the left; a removable splint on the right side supplying missing teeth with a raise on posterior extremity.

FIGURE 16. This illustration indicates our planned prosthesis. Note the improved bite and occlusion as compared with Figure 15. The upper right central tooth, which was infected, was removed and the other three anterior teeth were extracted for esthetic purposes. The results were gratifying.

FIGURE 17. This patient presented herself with a sharp, excruciating pain in the second division of the trigeminal nerve to the left side of the face. There is a noticeable prognathic action of the mandible caused by poor centric occlusion from poor dentures.

FIGURE 18. It is often said that all you have to show for your efforts are receipts. This lady was fortunate; she had several dentures to show for her unsuccessful efforts in trying to alleviate the pain.

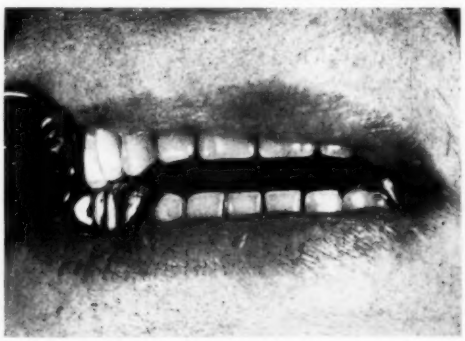


FIGURE 19. After proper correlation between the temporomandibular pictures and the occlusion, bite splints were attached to the lower denture, giving a balanced occlusion, relieving the pressure of the left condyle and gradually getting the patient to a more comfortable position.

FIGURE 20. The photograph shows the new dentures in balanced occlusion.

FIGURE 21. Our finished patient and case. She has had relief for over three years, and satisfaction is evident by the facial expression.

FIGURE 22 *(top)*. In February 1951 the patient presented himself with a pain of a sharp, excruciating, lancinating nature of the second and third divisions of the trigeminal nerve on the left. There was an ankylosis of the jaw on the left side which would not allow him to open his mouth beyond the extent of 2 mm. There was a history of surgical intervention—the posterior resection of a nerve root months prior to his appearance in the clinic. The malocclusion presented itself as an overbite of the upper anterior teeth over the lower: There were missing teeth on the upper and lower left arch; this was the affected side.

FIGURE 23 *(bottom)*. Splint in position, repositioning the mandible on both sides and increasing vertical dimension.

teeth are infected) so that healing does not interfere with reconstruction. Likewise the loss of additional natural tooth support will increase the subjective symptoms.

6. Condyle radiograms are studied with reference to position of occlusion.

7. Facial features are studied to determine the effects of occlusal wear.

Conclusions

It has been our observation that many patients describing sharp, shooting, knifelike pains throughout the face, produced in the act of washing, shaving, etc., present a clinical picture of severe dental malocclusion. There is not a full complement of teeth and those present are in a condition of abrasion and attrition. In edentulous cases there is a loss of vertical dimension.

The radiograms reveal the condyle in a posterior-superior displacement against the glenoid fossa.

Treatment consists of (1) increasing the vertical dimension, (2) replacing missing teeth and (3) establishing a new centric position.

The ideal reconstruction is not always attainable but our aim is to coordinate the occlusion so that there will be an existing harmonious relationship between movements of the teeth, the condyles within the glenoid fossa, and the musculature.

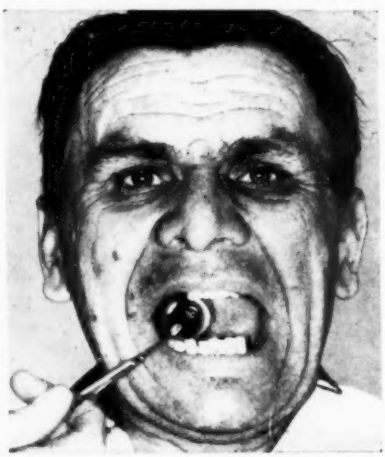


FIGURE 24 *(right)*. Photograph made after the patient had worn the appliance for four months. There is improved opening, enough to accommodate a dental mirror. This patient is free from pain; he has returned to work and now lives a normal life, is able to touch and wash his face.

Reticuloendotheliosis

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This article comprises a summary of the therapeutic results obtained by the use of nitrogen mustard as a supplementary measure in 6 cases of reticuloendotheliosis which may be classified in the group of normal cholesteremic lipidoses: Hand-Schüller-Christian disease, Letterer-Siwe's disease and eosinophilic granuloma.

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THE reticuloendotheliioses include a group of diseases of considerable interest: Gaucher's disease, Niemann-Pick disease, Hand-Schüller-Christian, Letterer-Siwe, eosinophilic granuloma and several less well defined clinical entities. The common characteristic in each of these syndromes is an accumulation of large, pale histiocytes usually containing a lipid. The specific lipid found in the phagocytic cells serves as one of the criteria for diagnosis and classification: Gaucher's disease—cerebroside; Niemann-Pick—phosphatide, and Hand-Schüller-Christian—cholesterol and its esters (Table 1). However, in Letterer-Siwe's disease, a nonlipoid type of reticuloendotheliosis, no lipid has been demonstrated. Absence of lipid has been reported also in eosinophilic granuloma.

On the basis of careful clinical observations together with pathologic studies, Wallgren, Letterer and Farber have concluded that the disturbance in lipid metabolism is a secondary, rather than a primary, factor in the pathogenesis. In view of these observations it seems reasonable to classify the Hand-Schüller-Christian syndrome, in which cholesterol or cholesterol esters are found in the histiocytes (a normal cholesteremic type of xanthomatosis), as one manifestation of the same basic metabolic disturbance which accounts for the clinical picture associated with eosinophilic granuloma and with Letterer-Siwe's disease—diffuse reticuloendotheliosis characterized by nonlipoid histiocytosis. These authors came to the conclusion that Letterer-Siwe's disease, which brings about the patient's death before the lipoid changes in the cells are marked, is a more malignant variant of the same pathologic process and that eosinophilic granuloma is to be considered a more benign form of the same basic disturbance.

The 6 cases reported in this discussion seem to fall into the latter group of diseases, each representing a slightly different phase of the same basic pathologic or metabolic disturbance. In patients showing manifestations of reticuloendotheliosis, spontaneous remissions may occur. With the exception of eosinophilic granuloma, however, prognosis is uncertain and in most instances the response to therapy has been a temporary one.

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Presented at the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

TABLE 1

CLASSIFICATION OF RETICULOENDOTHELIOSES

DISEASE	TYPE OF LIPOID SUBSTANCE	PATHOGNOMONIC FEATURES
Gaucher's	Cerebroside	Mottling of long bones, especially femur; rarefaction with cortical thinning. Flasklike appearance of ends of femur. Spleen markedly enlarged; liver moderately enlarged.
Niemann-Pick	Phosphatide	Any bone may be invaded by "foam cells." Spleen enlarged; liver markedly enlarged. Eyegrounds positive.
Hand-Schüller-Christian	Cholesterol and its esters	Defects in bones—membranous bones, characteristically. Diabetes insipidus. Exophthalmos. Skin rash in some cases. Liver and spleen may be enlarged.
Letterer-Siwe	Nonlipoid type	Bone defects similar to those of Hand-Schüller-Christian's disease. Spleen markedly enlarged; lymph nodes enlarged.
Eosinophilic granuloma of bone		Bone defect usually solitary—membranous bones or skull. Liver and spleen not enlarged, characteristically. Farber: Eosinophilic granuloma of the bone and Hand-Schüller-Christian disease "represent variations in degree, stage of involvement and localization of the same basic process."

In reviewing the therapeutic results of previous cases in our clinic, it seemed evident that while irradiation by x-ray had been beneficial in controlling local lesions of the xanthomatoses, the over-all results had not been consistently good. Certain reticuloendothelioses, mainly eosinophilic granuloma and Hand-Schüller-Christian's disease, did seem to show favorable response to deep x-ray therapy. With these facts in mind, the possibility of treatment with nitrogen mustard was considered. Since the nitrogen mustards affect cells by cytotoxic action in a manner similar to that resulting from irradiation by x-ray, and since experimental studies had indicated that the biologic activity of the two agents is remarkably similar, an attempt was made to evaluate the effectiveness of this type of treatment in patients who presented a clinical picture consistent with the diagnosis of reticuloendotheliosis, and in whom that diagnosis was verified by study of biopsy tissue.

In this evaluation of the possible efficacy of nitrogen mustard in the treatment of reticuloendotheliosis, we were encouraged also by its use in the treatment of other granulomatous disease states, particularly those of Hodgkin's disease and lymphosarcoma. A review of the recent literature reveals extensive reports which analyze the therapeutic effects of nitrogen mustard in patients suffering from a variety of diseases. The consensus seems general that while the nitrogen mustards are palliative and not curative, and in most instances no more effective than roentgen irradiation, they do have a definite place in the treatment of those diseases where rapid widespread effect is desired. As a rule irradiation by x-ray seems to be the therapy of choice where the disease is characterized by large local infiltrations. The most consistently favorable results have been obtained in the treatment of Hodgkin's disease and lymphosarcoma (Tables 2 and 3).

The present discussion comprises a summary of the therapeutic results obtained by

TABLE 2

USE OF NITROGEN MUSTARD (HN_2HCl) IN VARIOUS NEOPLASTIC DISEASES
(SUMMARY OF 210 PATIENTS TREATED FROM AUGUST 1946 TO MAY 1949) *

DISEASE	NUMBER OF CASES	LIVING	DEAD	TOTAL COURSES, USUALLY AS 4 INJECTIONS OF HN_2HCL
Hodgkin's disease	59	32	27	84
Carcinoma	35	23	12	44
Polycythemia	14	12	2	18
Lymphosarcoma	23	14	9	43
Other sarcomas	25	13	12	36
Leukemia, myeloid	9	5	4	11
Leukemia, lymphoid	16	6	10	21
Leukemia, monocytic	3	0	3	5
Leukemia, eosinophilic	2	1	1	2
Leukemia, acute blastic	2	0	2	2
Follicular lymphoblastoma	10	8	2	13
Mycosis fungoides	5	3	2	8
Miscellaneous	7	6	1	9
Totals	210	123	87	296
Total injections 1184				

*From Bauer, R. D. and Erf, L. A.: Clinical effect of nitrogen mustard on neoplastic diseases. Am. J. M. Sc. 219:16-26 (January) 1950.

TABLE 3

CHOICE OF THERAPY IN HODGKIN'S DISEASE*

X-RAY	NITROGEN MUSTARD
1. Localized lymphadenopathy in the peripheral, mediastinal or retroperitoneal region.	1. Widespread involvement.
2. Bone lesions.	2. Marked constitutional symptoms (fever, weight loss, etc.).
3. Obstructive lesions (great vessels, bile duct, ureters, spinal cord, etc.)	3. Fever without demonstrable enlarged nodes.
4. Fibrosing type of lesions.	4. Visceral involvement.
	5. Lesions "resistant" to x-ray.

*From Alpert, L. K., Greenspan, E. M. and Peterson, S. S.: Treatment of lymphomas and other neoplastic diseases with nitrogen mustard. Ann. Int. Med. 32:393-432 (March) 1950.

the use of nitrogen mustard as a supplementary measure in 6 cases of reticuloendotheliosis which may be classified in the group of normal cholesteremic lipidoses; Hand-Schüller-Christian disease, Letterer-Siwe's disease and eosinophilic granuloma.

Case Reports

Case 1—A 10 month old boy was seen in June 1948 (Figures 1 to 3). The salient features of his clinical picture at that time were a swelling on the head in the right occipital area, swelling of the jaw, and increase in mediastinal dullness. An x-ray revealed destructive lesions in the skull, in the seventh rib and in the long bones of the lower extremities. X-ray of the chest showed the presence of a mediastinal mass. Biopsy of the lesion involving the seventh rib and of the mass in the right occipital region was per-

FIGURE 1 (Case 1)

FIGURE 2 (Case 1)

FIGURE 3 (Case 1)

formed and examination indicated the presence of granulomas. Dr. Sidney Farber, who examined the specimens, described the lesion as characteristic of reticuloendotheliosis of the Letterer-Siwe type.

During the period between June 25 and July 27 deep x-ray therapy was administered over the various areas involved, a total of 9600 r in air. The patient showed no response to this treatment and was readmitted in August for a course of nitrogen mustard. The form used was methyl-bis amine hydrochloride given intravenously, 0.1 mg. per kilogram of body weight per day for four days, the total daily dose being 1.1 mg. One week following the termination of treatment he was transferred to the outpatient department. Since there was no significant change in the clinical course, the patient was readmitted on September 18 for a second course of nitrogen mustard therapy, which was identical to the first. From September 24 to October 26 the child was observed at weekly intervals in the outpatient department, following which he was readmitted for a second course of deep x-ray therapy (a total of 1180 r in air).

At the outpatient visit on November 16 the patient seemed markedly improved. Without further treatment the child has shown gradual and steady improvement. A series of x-rays taken during the spring months of 1949 revealed gradual filling-in of the old lesions and no evidence of new lesions. The general condition of the patient has improved and in January 1952 he was completely well with no evidence of skeletal involvement and no mediastinal involvement (Figures 4 to 7).

Case 2—A 20 month old white girl was seen first in November 1949. At 12 months of age she had developed a draining ear and a purpuric rash involving the entire body. The condition worsened gradually and the child was admitted to the hospital in December 1949. Examination at this time revealed an extremely malnourished child. Over the surface of the body there was an extensive skin eruption characterized by pinpoint lesions, red in color, which failed to blanch on pressure, and by larger lesions which were red to bronze in color. Yellowish crusts were present over the surface of the larger lesions. There was general lymphadenopathy; the spleen, palpable 5 cm. below the costal margin, was firm and smooth, and the liver extended approximately 5 cm. below the costal margin. Biopsy was performed for verification of the diagnosis of reticuloendotheliosis and the study was interpreted as showing a nonlipoid type of histiocytosis compatible with that seen in Letterer-Siwe's disease.

FIGURE 4 (Case 1)

FIGURE 5 (Case 1)

FIGURE 6 (Case 1)

Supportive treatment, including transfusions and nitrogen mustard therapy, was instituted, the first course of nitrogen mustard being the administration of 0.1 mg. per kilogram of body weight per day. The patient showed some improvement, appeared better clinically, ate well and seemed more alert. The skin lesions cleared almost completely and the patient seemed to be responding favorably to therapy. Improvement in the child's general condition was reflected in the next few weeks by improvement in appetite, gain in weight and decrease in irritability. There was no change, however, in the degree of hepatosplenomegaly. By the early part of January 1950 the skin lesions had reappeared, the patient was once more irritable, had poor appetite and showed loss in weight. At this time a second course of nitrogen mustard was administered, 0.1 mg. per kilogram of body weight per day. By the end of January the patient appeared markedly improved; the scalp lesions had disappeared; she appeared bright and intelligent and was in excellent spirits. However, while the general clinical impression implied favorable response to therapy, a survey of the skeleton revealed that there had been no change in the bony lesions. Between the months of December 1949 and June 1950, the time of discharge, this patient received six courses of nitrogen mustard.

FIGURE 7
(Case 1)

Dosage ranged from 0.1 mg. to 0.4 mg. per kilogram of body weight per day. While the skin lesions faded following therapy and the patient seemed to improve generally and to be more comfortable, there was no fundamental change in the basic condition. The patient died at her home in August 1950 (Figures 8 and 9).

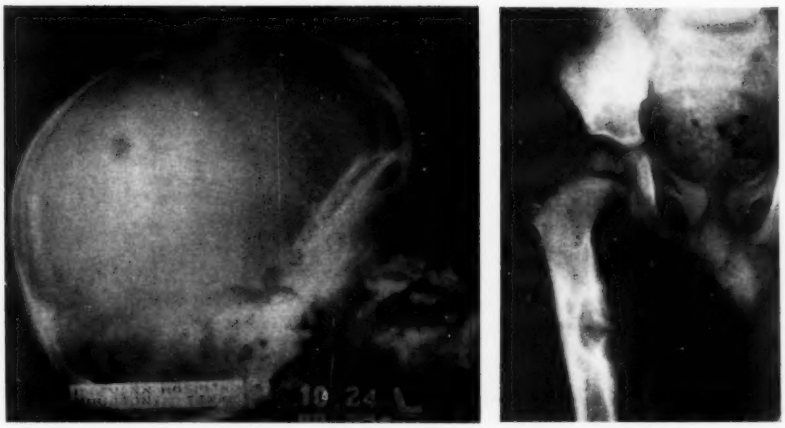
Case 3—A white boy, now 3 years of age, has been followed since he was 15 months old. He had had a nontender swelling in the right parietal region and had developed classic signs of diabetes insipidus. Biopsy showed the presence of eosinophilic granuloma. Deep x-ray therapy in this region re-

FIGURES 8 and 9
(Case 2)

sulted in complete healing of the lesion. Over the three year period he has done well on small daily doses of PITRESSIN® in oil. In the hope of altering the status of the diabetes insipidus, he was admitted to the hospital once during this period for treatment with nitrogen mustard, which was without effect.

Case 4—A white boy, 18 months of age, was first seen in October 1950, at which time he had a history of a scaling scalp rash since birth, and a mass over the right eye and a limp involving the left leg, both of six weeks' duration. About this same time the mother noted his increased thirst and increased urine volume. On admission there was general lymphadenopathy but no hepatomegaly and no splenomegaly. Motion of the left hip caused pain. X-rays of the skull revealed three sharply defined areas of rarefaction, marked destruction in the mastoid region and extensive destruction of the left ischium. Biopsy showed reticuloendotheliosis of the Hand-Schüller-Christian type. On October 30 the first of seven courses of nitrogen mustard therapy was initiated. The amount of the intravenously administered drug, measured in milligrams per kilogram of body weight per day, differed in each four day course, the first time being 0.1 mg. Following this treatment the skin showed a slight but not dramatic change in appearance. A second course of nitrogen mustard, 0.2 mg., was started on November 9. The skin condition improved gradually and the child seemed more comfortable. By the middle of November the tumor mass on the scalp had disappeared and improvement in the skin condition was definite. The patient was able to walk with no apparent discomfort and seemed to be feeling well. On November 24 a third course of nitrogen mustard, 0.3 mg., was given; again temporary improvement was noted. A fourth course was begun on December 27, 0.2 mg. The child appeared to be improved and continued to be cheerful, but the general outlook was not favorable. On February 7, 1951, a fifth course of treatment was started, 0.2 mg.; the sixth on February 19, 0.3 mg., and the seventh on March 6, 0.3 mg. During these weeks of treatment the fall in blood cell count was counteracted with blood transfusions. Despite apparent improvement the child died four months later, on July 7. The spleen was never palpable during the entire clinical course.

Case 5—A Negro girl, 17 months of age, was admitted to the hospital on February 13, 1951, and died within nine days following admission. On admission the child showed typical clinical manifestations of severe reticuloendotheliosis—skin rash, very large liver and spleen, and, on x-ray, bony destruction. Two courses of nitrogen mustard were given. The first, 0.1 mg. per kilogram of body weight per day for four days, was followed by slight



FIGURES 10 and 11
(Case 6)

general improvement; the second, 0.2 mg. per kilogram of body weight per day for four days, did not seem to affect the course of the disease. The patient died without showing any real response to therapy.

Case 6—A 2 year old white boy was admitted to the hospital on October 24, 1950 with a history of diabetes insipidus and destructive lesions of the skull, the right femur and ilium and the tenth left rib (Figures 10 and 11). Biopsy verified the clinical impression of reticuloendotheliosis. Nitrogen mustard was administered as follows: on October 30, 0.1 mg. per kilogram of body weight (1.1 mg. times 4); November 9, 0.2 mg. per kilogram of body weight (2.2 mg. times 4); November 24, 0.3 mg. per kilogram of body weight (3.3 mg. times 4), or a total of 26.4 mg. of nitrogen mustard. On this regimen the patient improved markedly in every respect. The white blood cell count, which fell to dangerously low levels, was controlled by blood transfusions. The polyuria and polydipsia, which remained unaltered, were controlled by the administration of pitressin tannate in oil.

At the time of discharge on February 22, 1951, the child showed marked improvement, definite evidence of healing being noted on x-ray of the bones. Observed as an outpatient he showed gradual improvement during the next few weeks; the diabetes insipidus was well controlled by small doses of pitressin tannate in oil. On March 31 a skeletal survey showed gratifying evidence of bone healing, especially when the x-rays were compared with those obtained on October 24, 1950. By May 19 further filling-in of the bony defects was observed. X-rays taken on September 27 showed continued healing of bone lesions, but on this occasion several new areas of involvement were noted in the skull (Figures 12 to 16). The patient was kept under close observation in the outpatient department. During the next few weeks he appeared well in general; however, a swelling was noted on the left side of the head in the temporal region, just in front of the ear. By November a skeletal survey revealed extension of the bony destruction in several areas, and readmission to the hospital was advised.

Consequently on November 19 the child was readmitted to Hermann Hospital. At the time of admission the patient seemed well, but the swelling in the left temporal region was definite, and the left eye was more prominent than normal (Figure 17). X-ray examination of the skull at this time revealed three new destructive lesions. The diabetes insipidus continued to be well controlled by means of small doses of pitressin tannate in oil, 0.3 to 0.5 cc. per day. On admission to the hospital the blood picture was as follows: hemoglobin 11 gm., red blood cell count 4,870,000, white blood cell count 8,450 with 1 stab, 74 segments, 24 lymphocytes and 4 monocytes.

Following blood transfusions for the con-

FIGURE 12 (Case 6)

FIGURE 13 (Case 6)

FIGURE 14 (Case 6)

trol of anemia, the administration of nitrogen mustard was initiated on November 20, 3.6 mg. intravenously daily for four successive days. For the next few days the patient appeared pale and listless; however, gradual general improvement followed and the lesion in the left temporal area decreased notably within one week. The white blood cell count, which had fallen to 1,850 on November 29, returned gradually to normal limits. The patient was discharged in good general condition on December 1.

This child has been seen regularly in the outpatient department and has shown gradual improvement. Survey of the skeleton on December 15 revealed further healing of the osseous lesions of the skull, and no new lesions were detected at that time. X-ray examination of the pelvis and hips showed the right ilium almost completely healed; similar studies of the lower extremities revealed no demonstrable osseous lesions. There has been continued improvement in this child; the diabetes insipidus is well controlled by the small doses of pitressin tannate in oil.

On January 19, 1952, the most recent examination, the boy appeared normal, in good general condition and seemed to have no complaints. A skeletal survey at that time revealed the following:

"*Skull:* Further filling-in of the lesion above the right orbit with only a small residual defect. Other lesions are too indistinct to outline at this time. There has been marked im-

FIGURE 15 (Case 6)

FIGURE 16 (Case 6)

FIGURE 17 (Case 6)

FIGURE 18 (Case 6)

FIGURE 19 (Case 6)

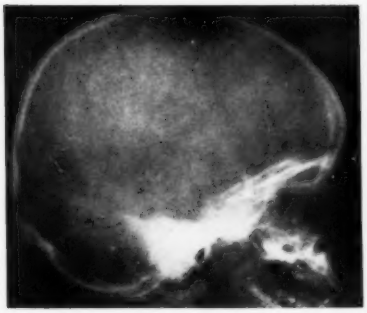


FIGURE 20 (Case 6)

provement, as is apparent on comparison of earlier films and those of December 1951 with the present.

"*Pelvis and both lower extremities:* There has been further filling-in of the defect in the right ilium; lesion is now difficult to identify. There is only one remaining small defect in the proximal femur. Excellent progression."

At that time the child was eating well and gaining weight. The diabetes insipidus, which had not been altered by nitrogen mustard therapy, was under good control (Figures 18 to 21).

FIGURE 21 (Case 6)

Summary

Clinical observation and x-ray studies on these patients suggest that nitrogen mustard does play some part in altering the course of reticuloendotheliosis, particularly in patients having marked skeletal involvement and minimal visceral involvement. In patients who succumbed eventually, improvement in the general condition of the patient seemed to follow the administration of nitrogen mustard; the child seemed to be more comfortable, had a better appetite, was more cheerful, and the skin lesions—while still present—as a rule seemed definitely less troublesome. Notwithstanding the temporary character of the improvement, the administration of nitrogen mustard would seem justifiable as a palliative therapeutic measure. In one case complete regression of the pathologic process seems to have occurred. In this instance a combination of nitrogen mustard and x-ray therapy was used. In a second case the patient is at the present time responding favorably in that a process of bone healing is taking place. In our experience symptoms due to diabetes insipidus are not improved by the administration of nitrogen mustard. Further clinical trials with this therapeutic agent, perhaps in combination with deep x-ray therapy, seem warranted.

DIAGNOSTIC CLINIC

Causalgia

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The pathologic mechanism involved in causalgia is discussed, and illustrative cases are reported. Treatment methods are described, and include blockade of the sympathetic chain and surgical procedures. Differential diagnosis of causalgia and hysterical post-traumatic vasomotor complexes is stressed.

CAUSALGIA is an unusual disease. The term was introduced into medical literature in 1872 by Dr. Weir Mitchell[1] to describe the burning pain which was the principal symptom presented by Civil War soldiers who had received nerve wounds. It is a euphonic term. Mitchell described very graphically the suffering that these patients underwent. He described men who had been valiant soldiers until they received an apparently minor wound and who thereafter began to complain of severe burning pain in the injured part. Following this, trophic changes would occur in the injured extremity to such a degree that it would be partially denuded, the nails would fall out and the part would become cold and clammy. Along with this would come an emotional deterioration so profound that if the pain persisted for a few weeks or months the patient would either become addicted to drugs or require incarceration in an institution for the insane.

Mitchell was unable to explain the pain mechanism. Many thought it was psychogenic, and this view is still held by some. Very little was added to our knowledge of this disorder until after World War I, when Leriche,[2] the great Frenchman, began to report his cases, in which sympathectomy had succeeded in controlling the pain. In the interval between World War I and World War 11 there appeared in the literature sporadic reports of patients either with injury to nerve trunks or perhaps with minor trauma to a part such as a digit who complained of pain apparently out of proportion to the amount of tissue damage. These, for the most part, had been treated—or mistreated, as you like—as psychoneurotics, though there were isolated reports by Homans, White, Spurling, deTakats and others of cure of causalgia by sympathectomy, confirming the observations of Leriche.

With the advent of World War II, neurosurgical centers were established in various Army and Navy hospitals in this country and also in the British Armed Forces, with the result that large numbers of patients with nerve injuries were observed by experienced neurologic surgeons. This gave an unusual

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Presented at the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

opportunity to study the disease of causalgia. It soon became apparent that it was a very common disorder and also a very remarkable one, and that the sympathetic nervous system was intimately involved in the production of pain.

During the war I had occasion to treat more than 3200 patients with peripheral nerve injuries, and of that group 105 suffered with causalgia. The opinions which I shall express were drawn largely from the experience with war wounded. However, I would emphasize that the disorder is by no means confined to military casualties. It is a very common sequel to trauma of any sort and presents a major and important problem in industrial accidents.

Many features of the disorder suggest that it is functional, and because of this many of these unfortunate individuals have unfairly been classed as psychoneurotics, and as the result of delayed treatment have undergone disabling emotional trauma and progressive ankylosis of the part of such degree that rehabilitation could not be accomplished, even when the pain was controlled.

The patients described by Weir Mitchell showed clinical evidence of ischemia. During the interval between World War I and World War II there appeared reports of patients with post-traumatic burning pain in whom the painful part was in vasoconstriction and ischemia was considered to be the mechanism of pain. Others reported cases in which the painful part was in vasodilatation, and the authors reporting these believed that the pain resulted from distention of the vascular tree. Tinel attributed the pain to infection in and about the wound. Leriche had thought it due at times to occlusion of some of the major vessels. Indeed, many theoretical explanations were offered concerning the etiology, but none would stand critical analysis.

It soon became apparent to me that while the subjective complaints were the same, the objective findings in these patients were of two types. In one, the affected extremity was cold and sweated excessively, the hair fell out, the skin was thin, and if one measured the blood flow of that part it was found to be in vasoconstriction and the blood flow reduced, with the result that the temperature of the skin, as measured by the thermocouple, was lower than that of the other side.

In the second group the involved part was in vasodilatation. The skin was dry, the hair was long and coarse, and the temperature of the affected part was elevated as compared with that of the normal side. Yet, in each group, interruption of the sympathetic chain supplying the painful extremity resulted in immediate cessation of pain, and the patient remained free of pain so long as the sympathetic blockade was effective. If surgical removal of the sympathetic chain was done, relief of pain was permanent.

We also observed that in no case in which the nerve was severed completely did the patient suffer such pain. It was only the patient whose nerve was hit and partially interrupted who developed this disorder. If the lesion was of sufficient degree to require the surgeon to cut out the injured block, then the pain disappeared.

If the patients went untreated for a prolonged period they tended to become emotional derelicts. They protected themselves from noises and any irritating stimuli. This evidence was confusing, and indeed those of us observing such patients were confused. We knew that sympathectomy would relieve the majority of them, but the cause of the disorder was not clear.

There is a story about a psychiatrist whose patient came in and said, "Doctor, I'm so nervous I don't know whether I am coming or going." The doctor examined him for a long time and then said, "You had better take your clothes off." He then examined him further and said, "You had better get yourself another doctor, because I don't know whether you are coming or going either." The situation was comparable to ours, for we were completely confused as to the cause.

During the war Doupe,[3] a Canadian, reviewed work done in neurophysiology previously by a group of Scandinavians—Granit, Leksell and Skoglund.[4] This work showed that in a normal nerve there is a constant interplay of impulses from one fiber to another. For instance, if in an animal one

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FIGURE 1. This patient was an infantry lieutenant who had been in continuous action with his troops, having marched over the Owen Stanley Mountains during the battle of New Guinea. He received three wounds without leaving his platoon. Then just a day or two before the final battle of Buna Mission was over, he received a 25 caliber bullet wound through his brachial plexus. Three weeks later he arrived in our ward, and I draw your attention to the facial expression, which reflects intense pain. His posture is impressive. Note that he holds his hand on a dry cloth of soft flannel and uses his good hand to prevent its moving. Even though this man had been overseas and away from his family for four years, he did not want to see them. He wanted to be in a dark, quiet room because any noise, even the tearing of a newspaper or the moving of a chair, would set off a paroxysm of unbearable pain. On one occasion a high-ranking officer from the Army Medical Department observed this soldier, and because of his crying, highly disturbed attitude mistook his condition for an emotional breakdown. He suggested this to the soldier, and the vituperative response of the soldier to the senior officer was not in the vein that is considered proper between a junior and a senior officer. Fortunately, the senior officer recognized his error and this ended the matter.

FIGURE 2. The same man, three weeks after sympathectomy was done. This young lieutenant then took over the direction of the rehabilitation center of an Army hospital and did an able job.

divided the anterior and posterior roots in the spinal canal and then stimulated the anterior roots, the impulses would be recovered from the distal end of the posterior root. It was generally thought that impulses could transfer only in the brain, but this work proved without question that there is a transfer of impulses within the nerve itself, evidently as the result of inadequate insulation of the nerve fibers in that nerve. Furthermore, it was shown that if the nerve of the animal was injured and the experiment then carried out, the transfer or shunt of impulses was remarkably increased. It appears probable that a short circuit such as this is the pathologic mechanism of causalgia. At least it is possible that the transfer of sympathetic impulses into an end organ destined to receive pain impulses may be responsible for the horrible suffering of patients with causalgia.

I am convinced that the alteration in blood flow is secondary to the pain and not the cause of it. Also it is likely that the trophic changes so often observed in the painful part are secondary to either ischemia or hyperemia. The exacerbation of pain by emotional stimuli is so profound that it is not surprising that many of these patients have been regarded as hysterical. When they awaken in the morning they usually feel pretty well, but after remaining awake for a while they begin to hurt. Indeed, any stimulus which would excite the hypothalamus would exaggerate the pain. Also, it has been well established that procaine injection of the sympathetic chain will interrupt the pain in causalgia, and if the period of relief following the injection coincides with the objective signs of an effective block, then sympathectomy may be done with assurance that the pain will be controlled.

FIGURE 3. Another case of causalgia, the patient being a Chinese soldier. From the photograph there can be no doubt that he had extreme pain. Note that the painful hand is held immobilized to avoid any movement or touch. This soldier would allow his bladder to become distended beyond all reason rather than void, for the act of micturition produced severe pain in his hand. Any sound, such as a squeak, also would induce severe pain. He discovered that he obtained relief when he immersed his hand in water. Subsequently we came to recognize that those patients with causalgia whose hands were in vasoconstriction would obtain relief when warm water was applied, whereas the pain would be exaggerated with cold water. The contrary was true when the affected part was in vasodilatation—cold water gave relief; warm water exaggerated the pain.

With this orientation concerning the history of causalgia, and the evidence which leads me to believe that the pathologic mechanism is a shunt of impulses from the sympathetic nervous system into sensory end organs in an injured nerve, I would like now to describe specific cases which I believe will color for you this clinical syndrome. Some will be patients who received war wounds, and others patients who sustained trauma in civilian life, in some cases apparently minor. In connection with these cases I will try to clarify the differential diagnosis between causalgia and other disorders and also to

FIGURE 4. This illustration and the two which follow are very dramatic. Note how this Chinese soldier protects his hand by covering it with his pajama sleeve. FIGURE 5. Relief from the causalgia is obtained following application of water to the affected part. FIGURE 6. Photograph taken a few weeks after sympathectomy was done.

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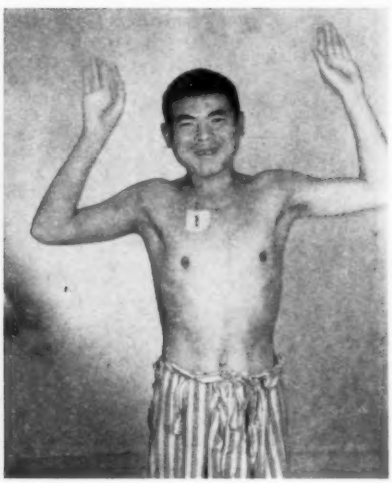

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FIGURE 7. A common observation in the wards—protection of the painful part with a soft flannel cloth. This was a patient who had sustained a median nerve injury—I think with a 22 caliber bullet. He would not permit anyone to separate him from the flannel cloth.

FIGURE 8. The puffiness, mottling and bluish discoloration associated with burning pain in this case occurred following a stab wound, with apparently minor injury to the sciatic nerve.

FIGURE 9. The hands of a patient with a median nerve injury. The extremity was in vasodilation. Note the excessive hair growth on the painful part.

FIGURE 10. Osteoporosis of the extremity in a case of causalgia. Much attention has been given to changes in bone which occur in painful states. In this case there is spotty osteoporosis present in the small bones of the foot of a patient who had sprained the ankle. It is not likely that the osteoporosis in itself is painful, as such a condition is seen at times in people who do not have pain. The pain probably is a secondary expression of altered blood flow.

FIGURE 11. The motor spasm associated with prolonged pain is striking. Here is a man who had sprained his hand a year before this photograph was made. He had no demonstrable bone injury and there was no significant swelling at the onset, but within a few weeks after the injury the pain began and became increasingly severe and was exaggerated by emotional excitement. He always kept his hand in this cramped, protected position because of pain. As a result he has actually drawn the carpal bones completely out of line, with the resulting deformity that you see.

clarify the relation of causalgia to the so-called minor causalgias, painful osteoporosis, Sudeck's atrophy, etc. (See accompanying illustrations.)

In addition to the illustrated cases, I would like to describe briefly the case of a nun who developed causalgia as the result of an injury to the median nerve by an intravenous needle. She was being operated on for spinal fusion, when the median nerve inadvertently was punctured at the antecubital fossa. There was tremendous atrophy of the hand. She did not have much actual paralysis. She could move

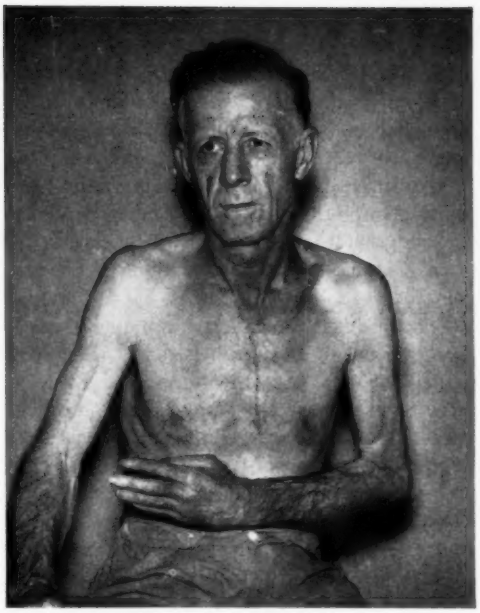

FIGURE 12. The subjective complaints and indeed the objective findings which occur as a result of a hysterical vasomotor complex are almost identical with those observed with true causalgia. Here, for instance, a man who had sustained a minor contusion thereafter protected his hand at all times because of severe pain. Notice that the fingers are straight and that they overlap the thumb. This is a position which usually is seen in hysteria. There is no organic nerve lesion which can produce this. As you know, the ulnar nerve extends the distal phalanges of the fingers, whereas the radial nerve extends the proximal phalanges. The median and ulnar together flex the fingers. So if either one of these were paralyzed or partially knocked out, there would be either a claw hand, a dropped wrist or the characteristic weakness of the index finger noted with median palsy. This man was involved in a claim for damages. Fortunately, in this instance, his disability was resolved by a PENTOTHAL® interview conducted by a skilled psychiatrist. This relief occurred even before the lawsuit was settled.

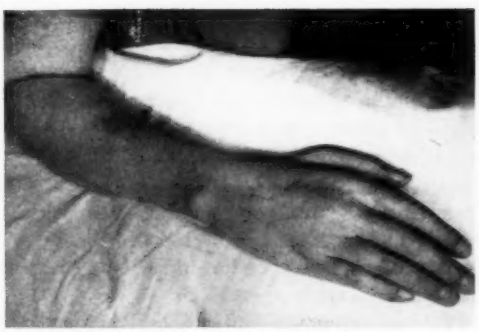

FIGURE 13. A hand similar to that seen in Figure 12. No organic nerve injury with which I am familiar can throw the hand into this position. Of course, if this persists for any protracted period of time, fibrous anklyosis will result.

(Figures 1, 2, 3, 7, 8, 9 and 10 are reproduced from: Mayfield, F. H. and Devine, J. W.: Causalgia. Surg., Gynec. & Obst., June 1945. Figures 4, 5 and 6 are reproduced from Woodhall, Barnes and Haymaker, Webb.[5])

her fingers a little, but in the autonomous zone of the median nerve there was subjective numbness and some hypalgesia. A series of procaine blocks with NOVOCAIN® were done, and on each occasion temporary relief would follow. Subsequently, however, sympathectomy was necessary in order to provide relief.

The patients illustrated in Figures 1 through 11 all sustained injuries involving some nerve or other. In the majority of instances the sciatic and/or median nerve was involved. The high incidence of causalgia associated with injuries to these two nerves probably is related to the fact that the percentage of sympathetic fibers in these two nerves is greater than in any other nerves. Each of these patients suffered severe pain, usually of a burning character, which appeared to be out of proportion to the amount of tissue damage. The pain was exaggerated by emotional stimuli and relieved by procaine injection of the sympathetic chain. Many patients with

this disorder recover spontaneously, and one is thoroughly justified in carrying out a series of procaine injections of the sympathetic chain, with the hope that the pain may be controlled sufficiently long to permit spontaneous recovery. On the other hand, when the pain is intense the hazards of emotional trauma and the dangers of ankylosis from disuse are so great that sympathectomy should be done early in order that they may be prevented.

Certain drugs are now available which may produce an effective blockade of the sympathetic chain. Among these are ETAMON CHLORIDE® (tetraethylammonium chloride) and PRISCOLINE® (2-benzyl-4,5-amidazoline hydrochloride). We frequently use these as a prelude to surgical attack on the sympathetic chain, in the hope that the disorder may be controlled without operative intervention.

Figures 12 and 13 illustrate the differential diagnosis between post-traumatic hysterical states and causalgia. There is only one way to distinguish between these two conditions, i.e., by procaine injection of the sympathetic chain. If one blockades with procaine that portion of the sympathetic chain supplying the painful extremity and relief follows when signs of block appear, and pain returns when evidence of physiologic block of the sympathetic chain disappears, then the patient has causalgia. On the other hand, those patients who obtain too prompt or too protracted relief from such a procedure must be regarded with considerable skepticism.

I have emphasized that causalgia may result from various types of injury, particularly those that occur in civilian life. I have drawn attention to a patient whose nerve was perforated by an intravenous needle. I have observed this disorder also on three occasions when orthopedic fixation pins perforated a nerve—one at the knee and two at the elbow. I have seen it on two or three occasions associated with injury to an intercostal nerve with a fracture of a rib. It is a very common complication with ankle or wrist sprains. One of the most difficult clinical problems I have encountered resulted from an injury sustained by a 14 year old girl when a basketball struck the end of her finger.

Summary

Causalgia is a painful disorder which develops following nerve injury, in which the patient usually complains of burning pain. It is associated also with profound trophic changes, which are believed to result from alterations in blood flow, which in turn is secondary to pain. It appears probable that the pathologic mechanism is a transfer or shunt of impulses at the site of injury within the nerve. It can be relieved temporarily by procaine injection of the sympathetic chain and permanently by surgical removal of the appropriate portion of the sympathetic chain. Relief also follows when the nerve injury is of such degree that surgical excision of the injured segment is necessary. Many patients with causalgia of mild degree recover spontaneously, and one is justified in using repeated procaine injections of the sympathetic chain or drugs such as etamon and priscoline, which blockade the sympathetic chain, so long as improvement follows, if the patient is not undergoing emotional deterioration or showing crippling ankylosis as the result of the pain. Procaine injection is essential in differential diagnosis between causalgia and hysterical post-traumatic vasomotor complexes.

There are a few patients with similar symptom complexes that do not result from either causalgia or hysteria. Their problem is most complex and not well understood, and time will not permit further discussion in reference to them. Fortunately, they are rare.

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SCIENTIFIC EXHIBIT

The Principal Cause of Breech and Transverse Presentations in Late Pregnancy

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INCIDENCE OF THE COMMON FETAL PRESENTATIONS IN SINGLE, TERM PREGNANCIES

	Per cent
Cephalic (all types)	96.3
Breech	2.9
Transverse, oblique or compound	0.8

Common General Placental Implantation Sites in the Term Uterus with Percentile Incidence of Occurrence

Sketches derived from anteroposterior and lateral soft-tissue placentographic x-rays of the term or near-term pregnant uterus

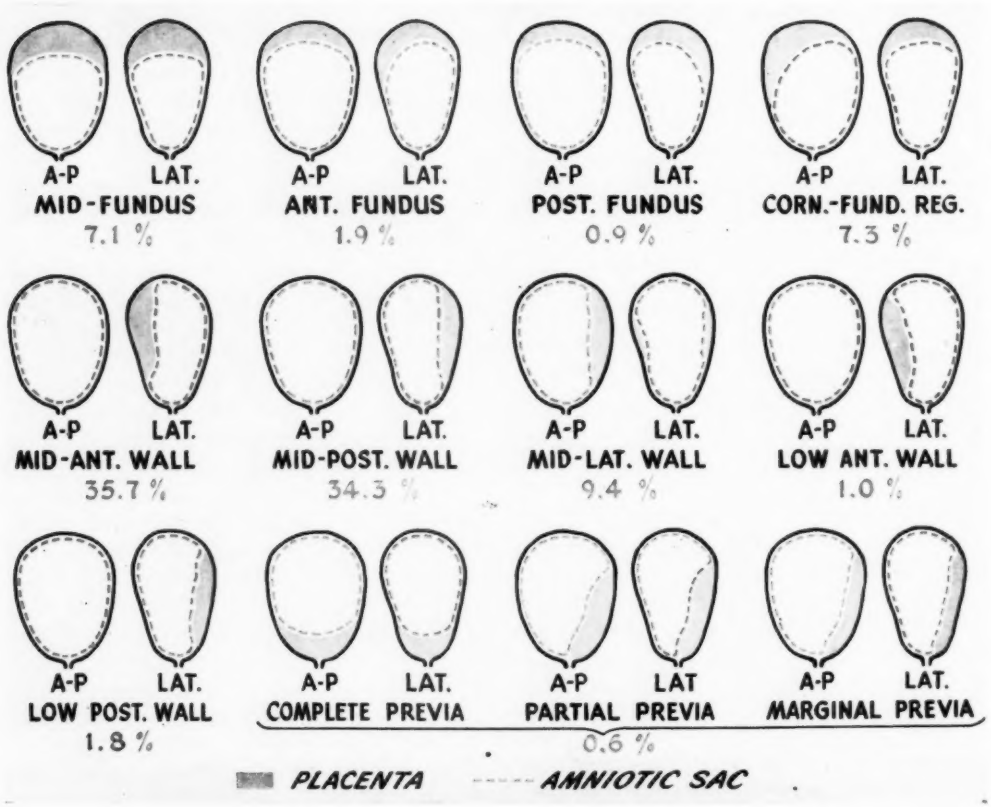

FIGURE 1. Note how *shape* of amniotic sac is determined by the position of the placenta. Also note that 10 per cent of all placentas are implanted either on the anterior or posterior wall of the uterus.

Cephalic presentation may occur when the placenta lies in any of the common implantation sites pictured (Figure 1), but breech presentation at term occurs only when the placenta is implanted in the cornual-fundal region on one side or the other, with few exceptions. Transverse or oblique presentation, in the last 10 weeks of pregnancy, occurs in 90 per cent of the cases only when the placenta is implanted in the fundus or is a "previa."

The human fetus, in single pregnancies, always tends to present *cephalically* and succeeds in doing so *unless some factor prevents it.*

TABLE 1

A Comparison of the General Placental Implantation Sites, Expressed in Percentage of Occurrence, in the Near-Term Uterus in a Series of Cases of Breech Presentation, a Series with Persistent Transverse or Oblique Presentation, and a Series in Which the Incidences of the Various Fetal Presentations Were of Relatively Normal Occurrence

Fetal Presentation	Mid-Fundus	Anterior Fundus	Posterior Fundus	Right Fundal-Cornual Region	Left Fundal-Cornual Region	Mid-Anterior Wall	Mid-Posterior Wall	Mid-Lateral Wall	Low Anterior Wall	Low Posterior Wall	Placenta Previa
All fetal presentations of normal average occurrence (681 cases)	7.1	1.9	0.9	"Tubenecken Placentae" 7.3		35.7	34.3	9.4	1.0	1.8	0.6
Breech presentation (76 cases)	0	0	0	29	71	0	0	0	0	0	0
Transverse or oblique presentation (52 cases)	25.0	15.4	5.8	0	2.0	7.6	0	0	11.6	5.8	26.8

Note above that the average occurrence of implantation of the placenta in the fundus of the uterus, regardless of fetal presentation, is 9.9 per cent, whereas in cases of transverse or oblique presentation the incidence is 46.2 per cent, and that only 3.4 per cent of placentas, generally, are implanted in the lower pole of the uterus, while in 44.2 per cent of the cases with transverse presentation the placenta was so implanted. The direct relationship between placental implantation in either pole of the uterus and transverse presentation of the fetus is obvious, and these particular placental sites have been shown to be the chief cause of this presentation.[1]

In the series of 76 cases of breech presentation the placenta was implanted only in one cornual region or the other, and such placental implantation site has been shown to be the principal cause of breech presentation in single pregnancies in the last weeks of gestation.[2]

1. Stevenson, C. S.: Transverse or oblique presentation of the fetus in the last ten weeks of pregnancy: Its causes, general nature and treatment. Am. J. Obst. & Gynec. 58:432, 1949.

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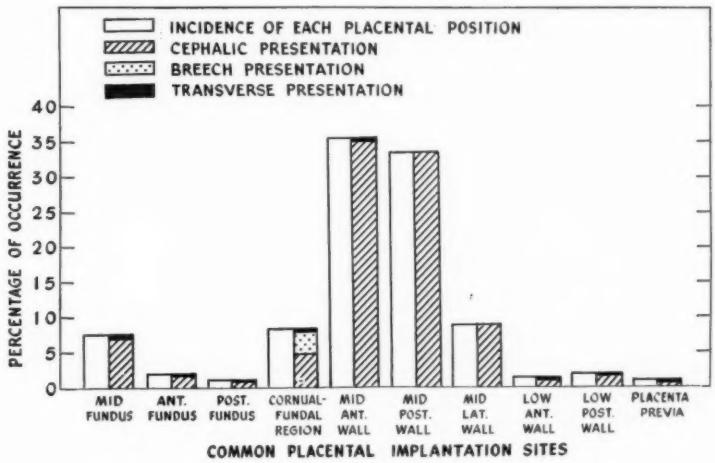


FIGURE 2. Incidence of the various placental positions and the fetal presentations common to them.

Why Does the Fetus Tend to Present Cephalically?

Is It an Effect of Gravity? No.

When one reviews the classic experiments of Duncan, Veit, Schatz and Seitz on the effect of gravity upon fetal presentation, one perceives that no definite causal role of this natural force could be established. Is the theory of accommodation valid? YES.

The theory of accommodation, as advanced by Dubois, Simpson, Scanzoni, Pinard and Sellheim, is undoubtedly correct in that the fetus accommodates its ovoid shape to the ovoid shape of the uterine cavity. With regard to the curled-up, ovoid fetus, as it lies within the uterus, its head is its smaller pole, its breech and legs the larger pole. The fetal head seeks the smaller pole of the uterine cavity, the lower uterine segment.

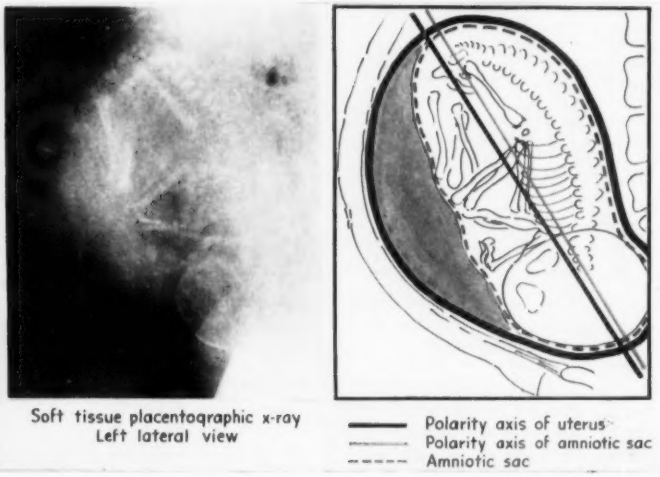


FIGURE 3. When the placenta is implanted on the anterior wall of the uterus, the fetal head seeks the lower uterine segment.

The sketch is a direct transparency tracing from the x-ray film on the left in this and subsequent figures.

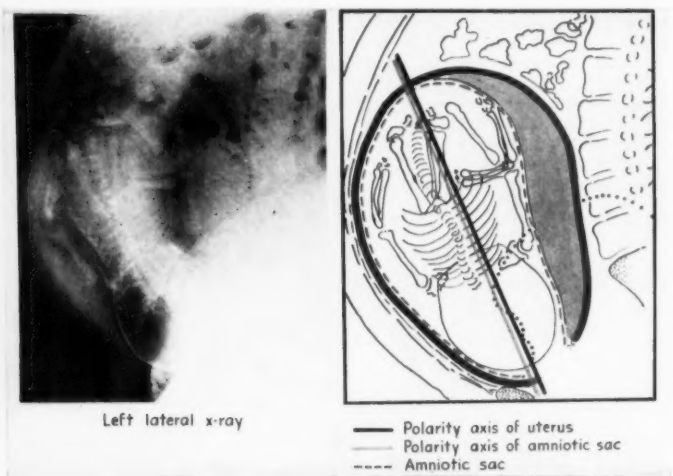
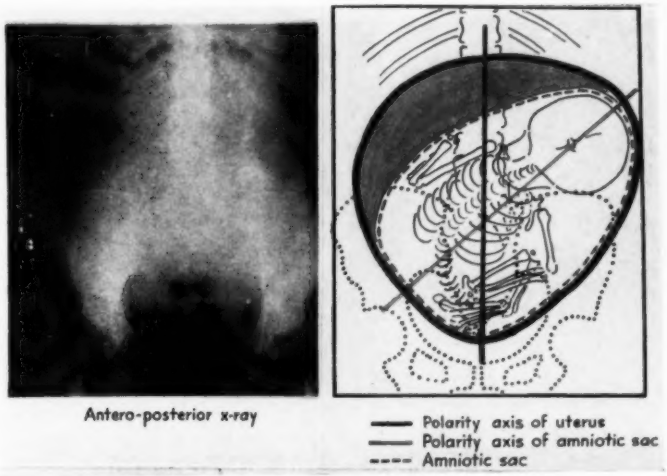


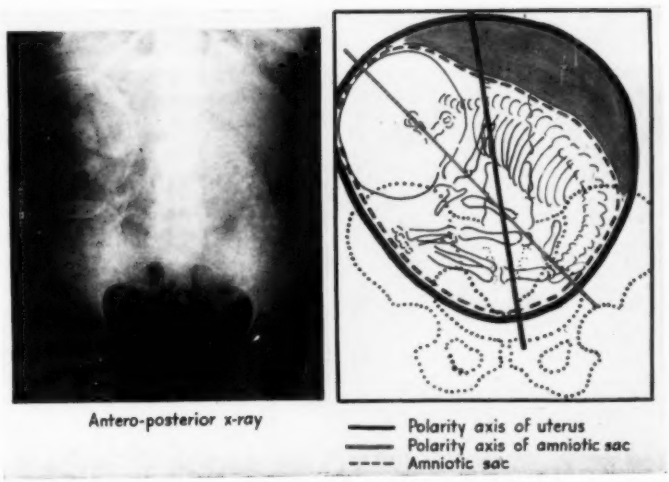
FIGURE 4. The fetal head likewise seeks the lower uterine segment when the placenta is implanted on the posterior uterine wall.

In the sketches (Figures 3 and 4) of anterior and posterior uterine wall implantation of the placenta one sees that the polarity axis of the amniotic sac is the same as that of the containing uterus, and that the fetal head lies in the smaller pole of the ovoid amniotic sac, which coincides with the smaller pole of the ovoid uterine cavity.

When the placenta is implanted over the lateral wall of the corpus uteri, or low on the anterior, posterior or lateral wall of the uterus, as in marginal and partial placenta previa, the fetal head again seeks the lower uterine segment, and thus when the placenta is implanted in any of these positions, cephalic presentation of the fetus results.

The Shape of the Amniotic Sac Is Determined by the Implantation Site of the Placenta, as shown in Figure 1





FIGURES 5 and 6. It is possible, in the case of certain placental sites, for the smaller pole of the ovoid amniotic sac *not* to lie in the smaller pole of the uterine cavity. Such is the case when the placenta is implanted in *the cornual-fundal* region of the uterus on either side.

One readily sees in Figures 5 and 6 that:

1. The placenta is implanted in the cornual-fundal region on one side, and

2. The opposite cornual region contains the small pole of the amniotic sac.

3. The fetal head lies in the smaller pole of the ovoid amniotic sac, as it has before, and

4. *Thus occurs breech presentation!*

Note that the polarity of the amniotic sac is independent of, and different from, the longitudinal polarity of the uterus.

The Effect of Cornual-Fundal Implantation of the Placenta in Causing Breech Presentation Can Manifest Itself in a Positive Manner

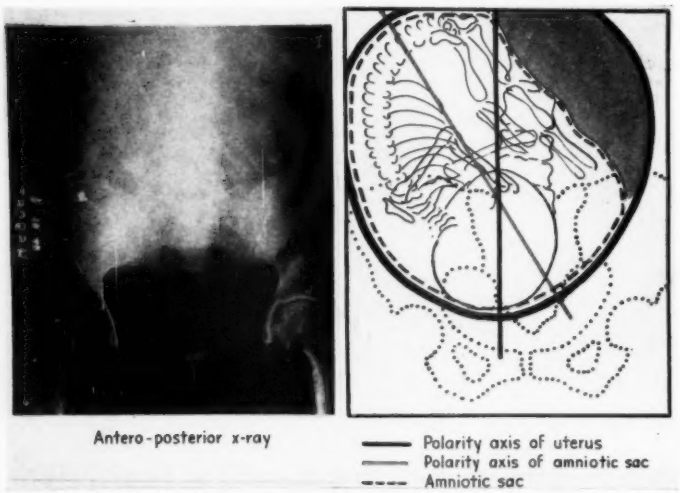


FIGURE 7. The x-ray was taken three days prior to delivery. It was predicted, because of the cornual-fundal implantation of the placenta, that the fetus might well undergo spontaneous version to breech presentation before the onset of labor. This patient, who was at term, returned to the hospital in labor three days later with the fetus presenting as a breech, and she was shortly delivered as a breech of a 2,870 gm. infant.

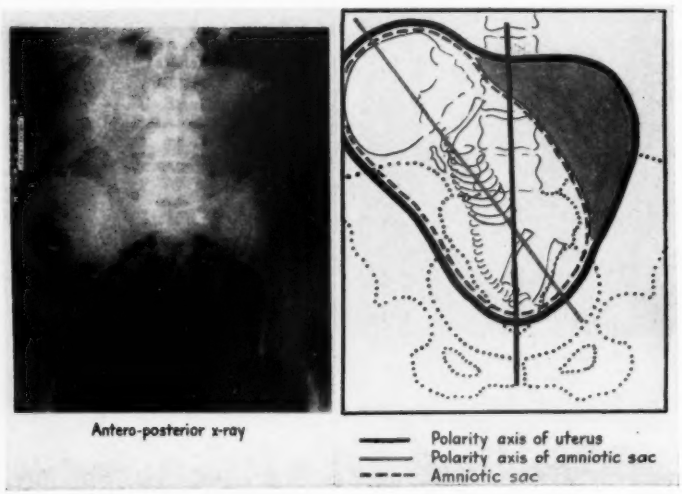


FIGURE 8. Bicornate uterus can be a causal factor in breech presentation, especially when the placenta is implanted in one horn of the uterus.

In all the x-rays (Figures 3 to 8) and their transparency sketches it has been evident that the fetal head seeks the smaller pole of the ovoid amniotic sac.

This appears to be a guiding principle in fetal accommodation to the shape of the available fetal space, that is, to the shape of the amniotic sac.

Transverse or Oblique Presentation of the Term or Near-Term Fetus Occurs, in 90 Per Cent of Cases, when the Placenta Is Implanted in the Fundus or in the Lower Uterine Segment, as in Placenta Previa Centralis

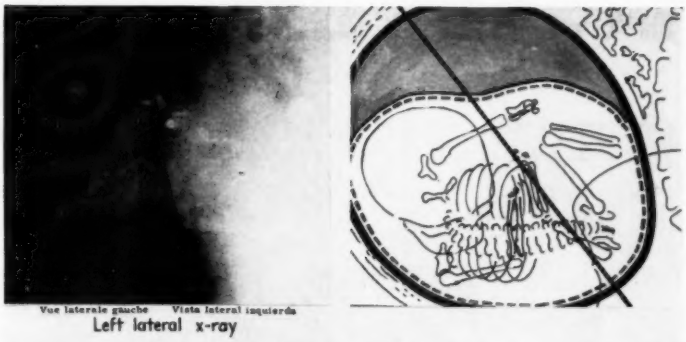
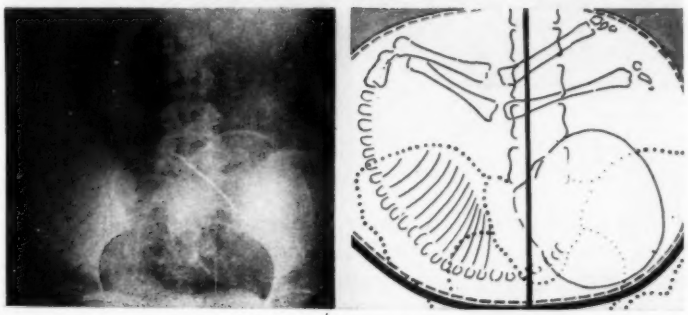


FIGURE 9. Mid-fundal implantation of the placenta.



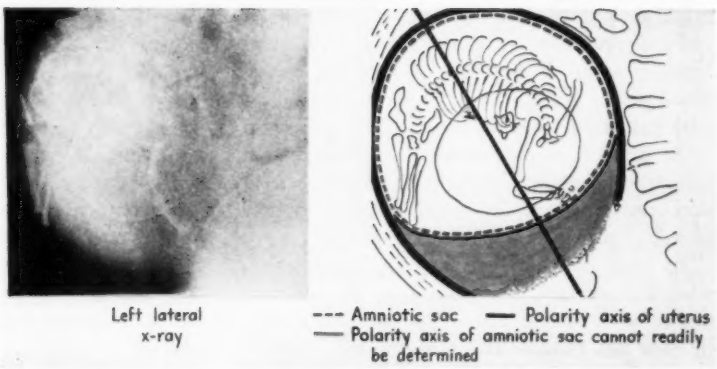


FIGURE 10. Central placenta previa.

The films in Figure 9 were taken of the same patient, the first being a left lateral view of the uterus and the second an anteroposterior view. Figure 10 includes a lateral view taken of a second patient. In these films it is apparent that:

1. The placenta is implanted in the fundus of the uterus in the first case and in the lower uterine segment (placenta previa centralis) in the second case.

2. There is no definite axial polarity of the amniotic sac (such as was present in the preceding cases), and the sac appears to be less ovoid and more spherical than when the placenta is implanted in other parts of the uterus.

3. The fetus lies transversely across the uterus in both cases, and

4. *Thus occurs transverse or oblique presentation!*

When the Placenta Is Implanted in the Fundus or in the Lower Uterine Segment, the Vertical Diameter of the Sac Practically Equals Its Transverse Diameter, and the Sac—Functionally Speaking—Becomes More Nearly Spherical Than Ovoid

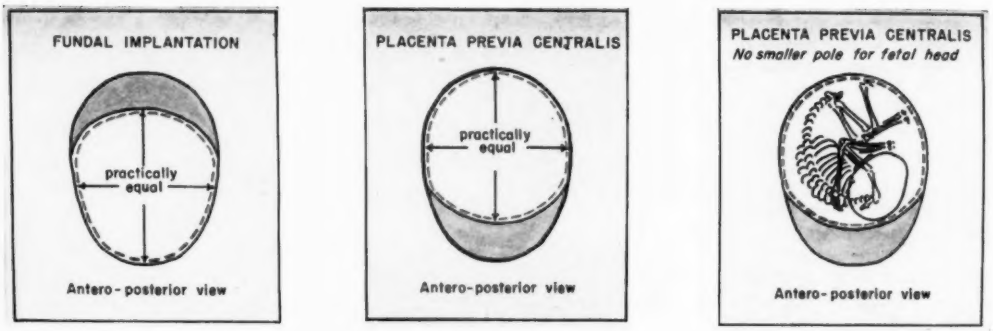


FIGURE 11.

The nearly spherical amniotic sac does not offer a smaller pole to the fetal head: The fetus curls up and accommodates itself as naturally as possible to the shape of the sac. Such accommodation results in transverse or oblique presentation of the fetus, at or near term, in about 28 per cent of all cases of placenta previa and in 3.5 per cent of all patients who have fundal implantation of the placenta.

As a result of our findings we believe that scientific proof has been given the old law of accommodation of the fetus, and that a new obstetric principle has been established:

In term or near-term human pregnancies, when the placenta is implanted on the anterior, posterior or lateral wall of the uterine cavity, it does not change the longitudinal polarity axis of the amniotic sac from that of the uterine cavity. But when the placenta is implanted chiefly in the fundus, lower uterine segment, or in either cornual region of the uterus, as it indents and alters the ovoid shape of the amniotic sac, it obliterates the polarity of the sac or determines it independently of the fixed polarity of the containing uterus. Functionally, the fetus accommodates itself to the shape of the sac, the fetal head seeking its smaller pole and the fetal breech and legs its larger pole. The *implantation site of the placenta* thus *determines* the *polarity and shape* of the *amniotic sac* and *hence*, through operation of the principle of fetal accommodation, *the presentation of the fetus.*

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Some Fundamentals of Ear, Nose and Throat Hygiene

RICHARD T. BARTON*

University of Southern California, Los Angeles

R. T. BARTON

THE physician serving in a large clinic or dispensary, especially one such as a student health service, finds himself repeating over and over certain fundamentals of hygiene. This advice, if followed, would prevent the patient much discomfort, which often is unwittingly self inflicted. It is my purpose to outline some of these rules of hygiene which are pertinent to the ear, nose and throat.

It has been my opportunity to serve as the otolaryngologist on four university health services. These represent a fair index of the entire country, as the institutions are located in the East (Harvard University), the Midwest (University of Chicago), and the Far West (University of Southern California and the University of California at Los Angeles). In each school the ear, nose and throat services are the second busiest, internal medicine being first in patient visits.[1] The incidence of ear, nose and throat afflictions is higher at the college age and in the college environment than in the general population.[2]

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Read before the Fifteenth Annual Meeting of the Pacific Coast Section of the American College Health Association at Occidental College, Los Angeles, California.

Hygiene of the Ear

Impacted cerumen—The old aphorism, "Nothing in your ear smaller than your elbow," is still good advice. Many patients have unnecessary ear difficulties because they fail to heed such wisdom. The first such difficulty is that of impacted cerumen in the ear canal. As the term implies, the cerumen is "packed" in the external ear, usually by the patient digging into the canal with his finger in an attempt to scoop out the secretion. As a rule he only pushes the so-called "wax" further in, beyond the isthmus of the external auditory canal and beyond retrieval (Figure 1). Because this condition is commonly found in people who are overly zealous about cleansing their ears, it has been called a "clean person's disease." Patients should be told that the normal ear canal does not need washing.

FIGURE 1. Diagram illustrating the finger packing cerumen further into the canal, while attempting to dig it out.

Removal of cerumen—Because of the sensitivity of the canal skin, cerumen should not be removed routinely by digging with "cerumen hooks." However, even irrigations can precipitate an external ear infection, if done roughly and if the syringe tip is allowed to lacerate the epithelium (Figure 2). Wash the ear with alcohol, if there is any question of external or middle ear infection or tympanic membrane perforation in addition to the impacted cerumen.

The itching ear—Our proverb about leaving the ear canal alone should be remembered with the itching ear also. Patients should be told never to dig in the ear with a bobby pin, a pencil or any other such weapon. How many hundreds of women have I seen with an ear canal swollen shut and exquisitely tender due to an otitis externa! They innocently explain that they "scratched the ear with a bobby pin, because it itched so badly!"

The itching ear is usually caused by a dermatitis of the canal, more often either seborrheic or eczematous; occasionally, when the canal appears normal, it may be caused by a nasal or eustachian tube allergy. The pruritus can be controlled best by using 70 per cent ethyl alcohol drops in the external ear or by antihistaminics in the case of allergy. Scratching with anything, even a cotton-tipped applicator, invites a painful inflammation of the ear canal.

Ear medications—It is my idea that ointments are a very poor vehicle for aural medication and should never be used except on the auricle. Ointments tend to accumulate, plugging the canal, and they never reach as far in the ear as do ear drops administered with the patient lying on his side. For the same reason, any powder should be blown into the ear very lightly, so as not to cake in the passageway. Analgesic drops are not nearly as effective as analgesics taken orally, but they occasionally are useful.

"Ear fungus"—During World War II we saw many cases of what was purported to be a "fungous infection of the ear." We still see many such cases. Often they are suppurative otitis media (either acute, chronic or acute exacerbations of chronic) or diffuse otitis externa (usually eczematous with or without secondary pyogenic infection). However, the successful treatment of otomycosis, like the successful treatment of mycotic infections of the feet and most other types of otitis, is based on the scrupulous avoidance of water. A patient with any kind of otitis externa should never get soap or water in his ears, even if the ears itch. Following this waterproof principle, 70 per cent ethyl alcohol ear drops will cure virtually all otomycoses and to use CRESATIN®, DESENEX®, etc. is to invite a sensitivity which is rarely justified.

Swimming with an ear infection—If one must swim in spite of a mild otitis externa,

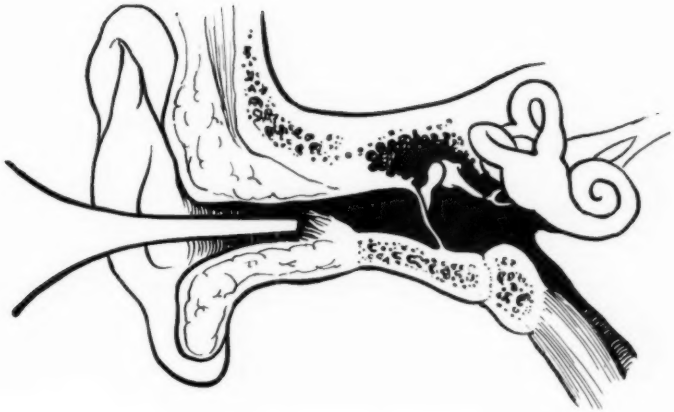

FIGURE 2. Diagram illustrating the irrigating syringe tip being inserted straight into the ear canal against the narrow isthmus and lacerating the thin epithelium overlying the bone.

such as in the case of water polo players during the regularly scheduled season, the ears should be dried afterward with 70 per cent alcohol drops. The use of ear plugs to prevent external or even middle ear infections is futile. Ear plugs are inadequate protection against otitis externa and media with tympanic membrane perforation. A patient with a known perforation should absolutely never swim! He should avoid getting water in his ear under any and all circumstances. Ear plugs offer little protection against middle ear injury from deep diving, surfboard riding, or underwater spear fishing. A traumatic perforation from the pressure on the external surface of the membrana tympani is less common than the injury caused by the water under pressure forcing open the eustachian tubes through the nose and contaminating the middle ear.

Drying the ears after swimming—If water is held in the external ear next to the drum after swimming (Figure 3) as a result of cerumen, exostoses or a narrow isthmus of the bony canal, the patient may attempt to remove it by dancing on one foot with the head tilted to the affected side or by jarring the head with a palm, but never by cupping

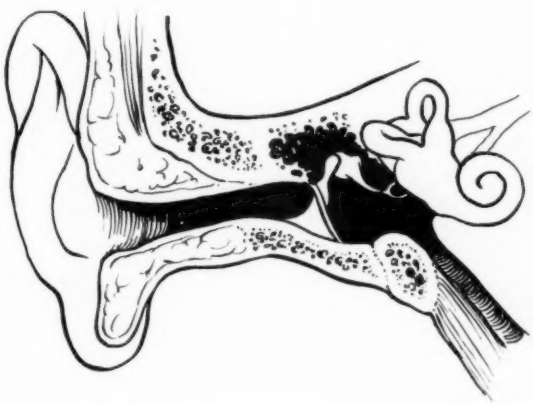

FIGURE 3. Diagram illustrating how water tends to puddle in the trough at the external auditory meatus against the tympanic membrane after swimming.

the ear with the hand and applying pressure or suction! If this jarring fails, a physician should remove the water by irrigating the ear with alcohol and drying with a cotton-tipped applicator.

Foreign bodies—The most common foreign body in the ear is a cotton plug lost by a self-treated patient. This would, of course, never occur had he followed the "Nothing in your ear smaller than your elbow" maxim.

Traumatic perforations—Traumatic perforations of the membrana tympani are painful, shocking and frightening. They should never be treated lightly, although the actual medical treatment is to leave them alone, to keep water out and to give an antibiotic prophylactically. The patient who has sustained a perforation from being slapped in the ear by an ocean wave, by a boxing partner or by his or her marital partner is likely to be most agitated over the injury and needs analgesics, sedatives and sympathetic reassurance. Medical services everywhere are frequently bitterly criticized because of the perfunctory handling of relatively minor traumas such as nasal fractures and traumatic perforations.

Hygiene of the Nose

"Vestibulitis digitorum"—The dictum, "Nothing in your ear smaller than your elbow" is equally true for the nose. Patients cause themselves a great deal of unnecessary suffering by picking or wiping the nose too vigorously. I am very fond of the term "vestibulitis digitorum," meaning an inflammation of the nasal vestibule from the digits or fingers, because of its accuracy. The various infections of the nasal vestibule, such as folliculitis and furunculosis, as well as most epistaxes are caused by manipulation with the finger or fingernail when wiping the nose.

Patients will persistently dig up into the nose beyond the mucocutaneous border and scrub the delicate mucosa to the point of bleeding or crusting. The blood clot or serous crust that thereafter forms is a good excuse for once again exploring far up "to get that stuff out, so I can breathe." Every rhinologist has seen patients who have picked a hole through the septum in this manner. College students, like children, are common victims of "vestibulitis digitorum," saying, "Doctor, I have to wipe way up in there or my nose does not feel completely dry!"

FIGURE 4. Illustration of how to wipe the nose properly with the finger wiping horizontally across the tip and not up into the vestibule.

Cauterization for epistaxis—It is the established practice to cauterize the Kisselbach plexus on the septum, which commonly bleeds from this type of nose picking and wiping. It is thought that cauterizing effectively destroys the bleeding vessels and prevents further epistaxis. However, it is my belief that more often the cauterizing agent, whether chemical or electrical, simply makes the nose so terribly sore and tender that the "chronic nose picker" leaves it alone long enough so it can heal spontaneously. The actual destruction of the blood vessel is irrelevant.

How to wipe the nose—Figure 4 demonstrates the proper way to wipe the nose. A horizontal movement should always be used and never a vertical one with the fingers up in the nares, as seen in Figures 5 and 6.

How to trim the nasal hair—If the vibrissae need trimming, it should be done only after soaking the scissors in ethyl alcohol and preparing the area by painting with aqueous ZEPHIRAN® or ethyl alcohol. A patient with cavernous sinus thrombophlebitis, who consulted me, precipitated the entire infection by plucking the vibrissae. She died 72 hours

FIGURE 5. Illustration of how *not* to wipe the nose (single digit technic) with the finger exploring far up into the nasal vestibule and even the nasal cavity.

FIGURE 6. Illustration of how *not* to wipe the nose (bimanual technic) with both index fingers simultaneously invading the nose far beyond the mucocutaneous border.

afterward, just 24 hours after treatment was instituted.

How to blow the nose—There is only one principle involved here, in spite of all the various "grandmother" rules: Never attempt to force air through a completely occluded nasal passage. To block an open nostril and force air through a congested one is dangerous. Vasoconstrictors must be used first before the occluded side is blown.

Nose drops—Nose drops almost never should be used. Vasoconstrictors and antihistaminics by mouth will open the nose in most cases, without nearly so much reactive vasodilatation. If such agents fail, however, nose drops may be used in the severely congested stages of an acute rhinitis. This is true of vasoconstricting inhalators or ointments, inhalators being most convenient for use in air travel.

One possible exception to the "no-nose-drops-in-chronic-rhinitis" rule is vasomotor rhinitis of pregnancy. This is often unaffected by oral medication, and nose drops are justified, as the nose invariably clears at the time of delivery.

"Cold shots"—Most patients that come to a doctor for relief from frequent colds are allergic, but in those patients that are not the problem of possible immunization is often presented. I have never seen any type of "cold vaccine" that was consistently effective, if effective at all. Cold shots and cold tablets are largely just "something to do," whereas a strict hygienic regimen of regular, adequate rest, good food with perhaps vitamin supplements, and a reasonable amount of exercise and recreation is more effective treatment, especially in college students.

Postnasal drip—Postnasal drip is normal! The normal nasal ciliary movement is for the most part backward into the nasopharynx, and it is in this way that the nose cleanses itself. One becomes aware of this "mucous blanket" when it becomes infected, as with a sinusitis, or when it becomes excessive or tenacious, as with chronic smoking. Tobacco is by far the worst offender, and the so-called drip will not clear up for a long time after the cessation of smoking. It is quite possible for the infected postnasal discharge of chronic sinusitis to cause bronchopulmonary disease and even gastric complaints of dyspepsia, but the lung and stomach symptoms associated with the postnasal drip of smoking are more likely to be due to the smoking itself than to the discharge.

Hygiene of the Throat

Antibiotic lozenges—Antibiotic lozenges

FIGURE 7. Illustration of the displacement of the mandible laterally by sitting for prolonged periods with the head cradled in the palm, resulting in "clicking" and "catching" of the jaw joint.

should never be used because of the high incidence of sensitivity. If the patient has an infection sufficiently severe to justify antibiotics or chemotherapy, he should have it in full doses and not in tiny amounts orally, as with troches. These are not enough to combat much infection, yet enough to sensitize. A patient who comes to the doctor with a mildly sore throat and ends up with a greatly aggravated one from a sensitivity to antibiotic lozenges will never understand the rationale of treatment.

Gingivitis—College students, many of whom are away from home for the first time, fall into some rather ridiculous habits. One such habit is the fanatical brushing of the teeth. Often they will scrub their teeth and gums to the point of bleeding and then consult a doctor about the gingivitis, fearing it to be "trench mouth" when it is purely traumatic, at least in its incipiency.

Temporomandibular arthralgia—Occasionally young scholars have another unhygienic habit, i. e., cradling their head in their palm for long hours while studying (Figure 7). This can cause a malocclusion and a traumatic arthritis of the temporomandibular joint. The patient rushes to the doctor complaining of a "painful catching" or a "clicking" in the ears or jaw joint when chewing or yawning. This is a typical college students' disease and vanishes when the head is supported by the neck alone while studying.

Infectious mononucleosis—Another condition which is most common in the college population is infectious mononucleosis. Where there are tonsils, there is a rather characteristic exudative membrane which has a gray, shaggy appearance with little erythema, not unlike a Vincent's infection but with a more pronounced cervical adenopathy. If, in the early stages of the infection, the characteristic cells are not seen in the blood smear, a lymphocytosis alone is highly suggestive. Later, of course, the heterophil agglutination test will be positive. There is no specific treatment; only supportive and symptomatic care is indicated.

Smoking—What is the effect of smoking on the nose and throat? Smoking can very definitely cause a characteristic pharyngitis and laryngitis. There is a typical diffuse hyperemia of the soft palate, pharynx and vocal cords, which will not show up in any "30 day test" but will in a "three year test." Smoking can cause the patient to complain of postnasal drip, frequent sore throat, dry cough and transient hoarseness. In my opinion, students in dramatics, speech and music (meaning voice), besides those in competitive sports, should not smoke.

Voice training—Many students who are referred by speech instructors or singing teachers have the basic problem simply of excessive smoking. Voice students often have a rather characteristic type of laryngitis—especially those who are forcing their voice or using their voice improperly by singing above their natural limits. They often will have small flamelike hemorrhages under the surface epithelium of the cords, or there may be a bright erythema of the medial or opposing edges of the true cords without any redness on the upper surface.

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The Recognition and Treatment of Vaginal Lesions

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WHENEVER there exist in the vagina a thick epithelium saturated in glycogen, a *p*H of 3.8 to 4.4 and abundant Döderlein bacilli, there is little chance for other organisms to grow. However, a *p*H between 5 and 7.8 lends itself readily to the growth of *Trichomonas vaginalis, Monilia albicans* and mixed infections. The presence of the latter organisms is not always accompanied by symptoms. Vaginal smears taken routinely may in 20 to 30 per cent of the cases show these organisms which may begin rapid growth and produce irritation. Besides the aforementioned organisms, we may have *Streptococcus, Staphylococcus* and gonococcus as invaders of the vagina. These other organisms are so frequently seen in trichomonas vaginitis that some writers believe the trichomonads are secondary invaders. There is no doubt that when the trichomonads disappear following treatment the other organisms disappear simultaneously.

Both trichomonal and mycotic infections occur during pregnancy when the *p*H of the vagina is on the alkaline side and also become activated during menstruation when the *p*H rises.

Whereas the history and treatment of the complaint may localize the seat of the trouble, it is the study of the smear which determines the actual invader or invaders. A hanging drop made with a mixture of the discharge and normal saline solution will demonstrate the organism either by its morphologic characteristics or by its movements. In some instances staining the material with special stains gives a better picture of the organism involved; in others, a culture of the discharge on Sabouraud's medium containing 15 units of penicillin will show the presence of *Monilia* organisms.

The patient seeks medical attention because of mild symptoms, such as leukorrhea with or without malodor. In acute cases, because of scalding sensations of the vagina, vulva and perineum, there may be intense itching, dyspareunia and burning and frequency of urination. When a patient presents herself with the symptoms described, a specimen should be obtained using a speculum without the use of a lubricant. The lubricant may interfere with the examination of the obtained material. After the material is obtained, the vulva, cervix and vagina should be inspected.

A frothy discharge containing air bubbles is present in trichomonas vaginitis and in many cases there are small amounts of blood.

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In the acute case the vagina is diffusely red; in the chronic case it may have a salt and pepper, granular or strawberry appearance, particularly on the cervix and the posterior fornix.

In *Monilia* infections the discharge may be very thick, thin, watery or purulent. On microscopic examination the fungus appears as a woven mycelium of long-branched filaments or hyphae; occasionally buds arise from the stem. The surface of the vagina is inflamed, and numerous white flakes are seen on vagina and cervix. Removing the flakes leaves a reddened surface. The vulva is frequently edematous. The *Monilia* infections are seen in diabetics because of the sugar in the urine and are not uncommon during pregnancy.

Treatment

Trichomonas vaginitis—There is no specific therapy and the infection may yield to a variety of methods and drugs. Chemotherapeutic drugs administered systemically have no value except when there is an accompanying bladder and rectum infestation. In general, the treatment consists of removing excess discharges, applying locally one of a variety of antiseptics, eradicating foci of infection, and preventing reinfection. One of the reasons for failure of cure is the stopping of treatment during the menstrual period. Before a patient is discharged as cured there should be active treatment through two or three menstrual periods and there should be three negative smears. Methods and substances for treatment of trichomonas vaginitis are listed in the table.

My preference in the treatment of trichomonas vaginitis is the use of an acid douche before retiring and the introduction of a suppository—any one of those mentioned in the table will be satisfactory. There may be some reaction to medication, particularly in the case of picric acid and arsenical compounds. The patient should be warned to stop the medication if there is a severe local reaction.

If the patient is in the active reproductive age, I prescribe an acid douche and one dozen suppositories to be used nightly beginning three to four days before the period and continued until all 12 are used. She is to continue the douches until four days before the next period and then begin the use of another dozen suppositories. Douches should not be used during the menstrual period. If there are three negative smears two weeks apart after the treatment just outlined, the patient should be considered as cured. If the smears are still positive one should look for the organisms in the cervix, Skene's ducts, urethra, bladder or rectum. Also, the husband should be examined. When the focus is found that particular nidus should be eliminated.

If the patient has a positive Kahn reaction arsenicals should not be used in the treatment for they may cause the syphilis to go into the latent stage.

The pregnant patient should be treated energetically up to the eighth month. It is best not to use powder insufflation during pregnancy.

Monilia infection—A good treatment is to paint the entire vagina, cervix and vulva with 2 per cent gentian violet and 1 per cent acriflavine in aqueous solution at least twice a

Douches (Acid)

Lactic acid—1 teaspoonful to 2 quarts of water
White vinegar—2 to 3 tablespoonsful to 2 quarts of water
Salt—2 teaspoonsful to 2 quarts of water

Powder Insufflation

FLORAQUIN® powder
Kaolin with 1 per cent silver nitrate
VIOFORM®
AUREOMYCIN®

Suppositories

Picric acid
Carbarsone
Sulfonamides
Antibiotics—aureomycin, terramycin, etc.

Tablets

Floraquin
Glucose, lactose and boric acid, 5 gr. each
Vioform

Vaginal Jellies

Any contraceptive jelly
Acid jel

week. Or an acid jelly or a gentian violet jelly may be used nightly.

Vulvovaginitis of the infant—A profuse discharge from the vagina in the infant is best treated by organotherapy. One should introduce into the vagina a small, narrow suppository containing 0.5 mg. of stilbestrol nightly for two weeks. If after three weeks there is still a discharge the vagina should be explored with a direct vision Kelly cystoscope to see whether the vagina contains a foreign body. If a foreign body is present its removal will clear up the discharge.

Senile vaginitis—The absence of estrogenic hormone produces an atrophy of the mucous membrane. This change permits pathogenic organisms to take hold, producing a marked burning discharge with mottled red spots, excoriations and watering of the tissues. In the marked cases there are adhesions between the anterior and posterior walls of the vagina which cause retention of pus pockets. Under gas the adhesions should be broken up making the vagina one continuous cavity. This should be followed by lactic acid douches and either oral or local estrogenic therapy. My preference is the local use of 1 mg. stilbestrol suppositories nightly for two to three weeks.

Condylomas—This condition may be either the flat, moist papule of luetic origin (the condylomata lata), or tiny papillary tufts to cauliflower masses (the condyloma acuminatum, the result of poor sanitation). The former should be treated as any secondary syphilis and the latter should be treated with cleansing douches and 25 per cent podophyllin in mineral oil in the small lesions. Cauterization, fulguration or surgery should be used for the larger masses.

Vaginal cyst—Most of these cysts are inclusion cysts due to inverted squamous epithelium following a surgical procedure, or buried mucous membrane following a vaginal tear at delivery. They are usually situated near the vaginal introitus. If small they may be destroyed with the nasal tip cautery or removed surgically.

Gartner's cyst—The lower end of the wolffian duct which passes from its course in the mesosalpinx downward along the uterus and vagina may give rise to cysts in the terminal vaginal portions, on the lateral walls, the floor of the vagina or the vesicovaginal septum. They are practically always benign and should be removed surgically. Extreme care should be used in removing those in the bladder area or rectovaginal septum because of their proximity to the bladder and rectum.

Endometrial cyst—These cysts are more common than described. Most often they are located in the posterior fornix. They are bluish or purple in color and usually contain blood. The location of the cyst in this area is usually an expression of other endometrioses in the pelvis. The local lesions may be destroyed by the cautery or removed surgically.

Polyp—Polyps of the vaginal vault are not rare following total abdominal or vaginal hysterectomy. They may be found anywhere in the scar area but are found more often in the lateral corners. They frequently become infected and bleed. They are removed by the actual cautery and rarely return. Occasionally there is found a polyp formed by the protrusion of the infundibular end of the fallopian tube through an imperfect closure of the peritoneum and vaginal mucous membrane. The infection should be cleared up and the tube drawn down as far as possible; it may be ligated and cut or removed by cautery. The stump is allowed to be drawn up into the abdominal cavity. Suturing of the vault is unnecessary.

Lesions of Vaginal Portion of Cervix Uteri

Erosion—Cervical erosions are very common, particularly following childbirth, and are usually the result of irritating discharge followed by inflammation. This causes exfoliation of squamous epithelium followed by repair. As the denuded area is covered by high columnar epithelium, removal of the irritant in many cases is sufficient for spontaneous healing. A lukewarm douche twice daily with tincture of iodine or lactic acid, 1 teaspoonful to the quart, may be helpful. If this does not aid the healing process, the use of the nasal tip cautery is indicated. During men-

strual life it is best to use the cautery four or five days postmenstrual to permit healing before the hyperemia of the next menses. Postcauterization healing may be hastened by the use of sulfonamide ointment applied locally to the cauterized area. The involved area always should be studied for the possibilities of malignancy by the Papanicolaou smear or biopsy, particularly in cervical erosion occurring close to or past the menopause.

Multiple nabothian cyst—These cysts of the cervix may be destroyed by cauterization with the nasal tip cautery. They are bluish white, semitranslucent areas which on puncture yield a glairy mucus. Occasionally there is a retention cyst cervical polyp which can be removed with the cautery.

The typical cervical polyp arising from the endocervix is a strawberry-like mass, reddish in color, which bleeds readily upon irritation. Leukorrhea and contact bleeding bring the patient to the physician. Such polyps are rarely malignant and can be removed very effectively with the nasal tip cautery, particular attention being paid to the base of the polyp. All polyps removed, especially those of long standing, should be sent to the laboratory for pathologic study.

Lacerated cervices and everted cervices or ectropion should be corrected by surgical means. This is done by cutting out the unilateral or bilateral tear and bringing the edges of the raw surfaces together. Care should be taken to prevent strictured cervical canals by sounding them occasionally.

At this point I would like to state that treatment of most cervical lesions by the use of electrocoagulation, conization or Sturmdorf's operation can be accomplished with the nasal tip cautery without some of the sequelae following the former procedures, such as atresia of canal, hemorrhage or leukorrhea. Most cauterizations can be done in the office, thus reducing the financial burden to the patient. During menstrual life cauterization should be done four days postmenstrual and not in the presence of an acute infection.

Finally, any suspicious lesion on the cervix must be biopsied before any attempt at treatment in order not to mask malignancies and granulomas.

BREATHING

THE lung is always full of a quantity of air, even when it has driven out the air which is necessary for its exhalation; and when it is refreshed by new air it presses on the sides of the chest, dilates them a little and pushes them outwards, for as may be seen and felt by placing the hand upon the chest during its breathing, the chest expands and contracts, and even more so when one heaves a sigh. For nature has so willed that this force should be created in the ribs of the chest and not in the membrane that ends the substance of the lung, lest by an excessive ingathering of air in order to form some unusually deep sigh this membrane may come to break and burst itself.

Leonardo Da Vinci (1452-1519)

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Recurrent Convulsions in Children

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CONVULSIVE disorders present an important challenge to physicians responsible for the care of children. The problems of diagnosis and successful treatment are multiplied by the variability of seizures in children and of their response to anticonvulsant therapy. The causes of convulsions among children are more diversified than among adults. genetic factors play a larger role[1] and the prognosis, with all its implications, is more uncertain. The calamity of the first convulsion represents a major tragedy to the parents and requires patient understanding and interpretation by the physician, while the psychologic and social problems presented by the child with recurrent attacks may necessitate expert assistance from several allied disciplines over a period of years.

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Etiology

The importance of heredity in the etiology of epilepsy has been well established;[2-4] however, it is also evident that the onset of recurrent seizures is due to various acquired conditions in combination with the convulsive diathesis. The basic determinant is an alteration of neuronal activity originating from disturbances of physicochemical function, the nature of which is not clearly understood and which is beyond the scope of this discussion.

The relative significance of various etiologic factors in childhood epilepsy depends on the age of the patient.[5-8] More than half of the convulsions which occur below the age of 6 months result from congenital defects and cerebral trauma complemented by acute infections. Between the ages of 6 months and 4 years, convulsions associated with intracranial and extracranial infections increase proportionately, although the introduction of antibiotic therapy has now reduced the incidence of convulsions associated with acute or chronic infections. About 2 per cent of infants who develop attacks during the first month of life

have idiopathic epilepsy;[5] however, this diagnosis is usually made by exclusion and must be determined in retrospect later in life. The proportionate incidence of genetic epilepsy increases progressively throughout childhood and adolescence, so that more than half of the convulsive disorders observed at 16 years of age are due to idiopathic epilepsy. Tetany occurs in the newborn, but reaches its peak from the age of 3 months to 3 years, then gradually declines.[5] Other causes of recurrent convulsions include spontaneous hypoglycemia, brain tumors, subdural hematomas, uremia, chronic toxic encephalopathies, degenerative neuropathies and postnatal hemorrhage or trauma.

The contribution of febrile convulsions to adult epilepsy has been well established.[9-14] The incidence of convulsions in otherwise normal children under 5 years of age has been estimated at 4 to 7 per cent.[9,10] The majority are benign, occurring in response to an abrupt rise in body temperature accompanying acute infection; however, later in life 5 to 10 per cent of these children will develop recurrent attacks without fever.[12,19] Important prognostic signs include a severe or prolonged initial attack or multiple convulsions, onset early in infancy, focal signs, severe or persistent electroencephalographic changes and a family history of epilepsy.[9,12] Various investigators have found a preponderance of febrile convulsions in males, although idiopathic epilepsy occurs more frequently in females.[12,13] Livingston, Bridge and Kajdi[14] reported that all children who develop convulsions in response only to fever early in life recover by the age of 8 years. Other authors have reported the onset of epilepsy after an interval ranging from a few months to 25 years, with 40 per cent experiencing free periods of 10 years or longer.[9,12]

The significance of prolonged delivery, birth injury or neonatal asphyxia in the etiology of epilepsy remains controversial. Most authors agree that these factors are extremely important. Russ and Strong,[15] from a survey of more than 1200 cases, stated that serious changes would result from postnatal anoxemia of more than two minutes' duration. Keith,[16] studying 4,411 deliveries, concluded that prolonged labor and asphyxia appeared to increase the risk of intracranial injury and death; however, if the infant survived, there was no residual impairment which disturbed normal subsequent development. In his report, follow-up studies included only the first few years of life. Nielsen and Courville,[17] studying 956 epileptics of whom 39 per cent were first-born, concluded from both clinical and pathologic studies that idiopathic epilepsy is due to small focal areas of cortical damage to individuals with lowered convulsive thresholds. Their results indicate that first-born children are twice as susceptible to injury as are children born subsequently to the same mothers. After a few weeks, focal lesions are present, consisting of innumerable very small or microscopic areas of necrosis, which are replaced after several months by focal cortical scars and cysts. The authors have observed microgyria after many years, a finding which has been confirmed by Penfield[18] who believes them to be a potential site of origin for convulsive disturbances.

Classification

Adequate anticonvulsant therapy in children depends foremost on accurate diagnosis and classification. Children are more apt to have a single type of seizure than adults,[19] perhaps due to the fact that petit mal is primarily a disorder of childhood. The existence of combined or multiple forms of epilepsy is a poor prognostic sign because of the increased difficulty of medical management. Generalized convulsions or grand mal seizures constitute the largest proportion of attacks in children. Focal signs are not apparent as often in children as in adults, due in part to the difficulty of obtaining a history of subjective disturbances. Focal motor attacks frequently have inconstant patterns, lacking the classic progression or "march" of the jacksonian seizure.[19] Transient paralysis of one or more extremities—so-called Todd's paralysis—may result from individual attacks. When this occurs, even following isolated febrile convulsions, intensive therapy is indicated to prevent subsequent attacks which may

result in permanent paralysis.

Focal aura or minor focal cortical seizures may consist primarily of sensory or motor phenomena, depending on the localization of the abnormal neuronal activity. They must be distinguished from petit mal as it is commonly and erroneously conceived. They have been described and classified in detail by Penfield and co-workers.[20,23]

Penfield[20] and Gibbs[21] have demonstrated conclusively that psychomotor seizures, also known as psychic equivalent attacks, are a type of focal epilepsy originating in the temporal region. They occur less frequently in children; in a series of epileptics reported by Lennox[22] only 10 per cent of children below the age of 10 years had psychomotor attacks, compared with 34 per cent of persons 40 years of age or older. Psychomotor attacks may be difficult to recognize in children; they consist of varying degrees of altered consciousness associated with purposeful but irrational behavior. Postictally, the patient is unable to recall the events that have taken place and may not be aware that an attack has occurred. Psychomotor attacks may be preceded by psychic aura and followed by fatigue and malaise. They usually occur every few days to weeks, in contrast to petit mal which generally occurs many times a day.

Petit mal epilepsy is principally a disorder of childhood. Of 1,260 epileptics studied by Gibbs, Gibbs and Lennox in 1943,[24] 42 per cent were under 20 years of age; of those having petit mal exclusively, 84 per cent were below the age of 20. Petit mal seizures have a common basis in the spike and wave dysrhythmia in the electroencephalogram and in the favorable therapeutic response to the oxazolidine-diones such as TRIDIONE® or PARADIONE®.[25]

There are three main types of petit mal seizures which constitute the petit mal triad: pyknolepsy, akinetic seizures and myoclonic jerks.

"Pure" petit mal (pyknolepsy) consists of a brief lapse of consciousness accompanied only by slight rhythmic movements such as blinking the eyes, raising the eyebrows, chewing motions or shrugging the shoulders. The lapse of consciousness is usually brief, occurs without warning and is not followed by after-symptoms. As a rule, attacks recur many times a day.

Akinetic seizures, originally described as "static" attacks by Hunt,[26] are characterized by sudden loss of postural tone, with falling, and usually are accompanied by only a fleeting lapse of consciousness.

Myoclonic jerks consist of single, lightning-like flexion contractions of one or both arms without loss of consciousness. They rarely occur without a history of other forms of petit mal, but may easily be confused with habit spasms or chorea. An uncommon type of attack is the massive myoclonic jerk observed almost exclusively in brain-damaged children and before the age of 3 years.[27] These seizures consist of flexion and abduction of the arms associated with tonic flexion or extension of the legs; they may occur singly or in a slow rhythmic series lasting as long as one minute. Such attacks carry a poorer prognosis than do other types of petit mal because of their frequent association with brain damage and poor response to anticonvulsants. Although they usually disappear by the age of 4 years, they are replaced by mixed types of seizures.[27]

Obviously, the simple classification outlined is not always applicable. For instance, atypical petit mal episodes may be clinically indistinguishable from psychomotor attacks. Bizarre, minor seizures may be accompanied by a petit mal variant dysrhythmia or by a preponderance of spike activity in the temporal regions.[22,27]

A number of "borderland" conditions whose relationship to epilepsy is poorly defined occur in children. These include prolonged periods of unconsciousness without tonic or clonic activity; paroxysmal bouts of abdominal pain, with or without vomiting, referred to as "abdominal epilepsy";[28-30] periods of unexplained high fever sometimes accompanied by alterations of consciousness, and a variety of psychic phenomena such as temper tantrums, sudden self-limited behavioral changes or night terrors. The clue to many problems lies in the properly recorded, correctly interpreted electroencephalogram.

One of the most provocative problems presented by children subject to seizures is that of breath-holding spells. They usually begin at the age of 12 to 18 months—rarely beyond the age of 2 years—and usually disappear by the age of 5 years. In some cases, the spells occur in direct response to trauma or temper tantrums. During violent crying sudden breath-holding associated with cyanosis occurs. Loss of consciousness may follow; infrequently there is convulsive activity. In other children the spells are provoked by simple startling or by a slight blow. The latter group suggests that a different mechanism may be responsible, the startle reaction serving merely as a trigger mechanism to provoke latent epilepsy.

Breath-holding may also be misinterpreted as an emotional disturbance rather than as the apnea associated with tonic spasm at the onset of a generalized convulsion. Kanner[31] reports that 51 of 188 infants examined in a well baby clinic were said to have breath-holding spells or a history of same; cyanosis occurred in 18 per cent, and unconsciousness and convulsions each occurred in 2 per cent. Bridge, et al.[32] reported cyanosis in 93 per cent, loss of consciousness in 60 per cent and convulsions in 49 per cent of 83 children who were brought to the hospital with the specific complaint of breath-holding spells. Three developed definite epilepsy later in life. Children who experience loss of consciousness and convulsive movements with breath-holding spells may respond favorably to anticonvulsant therapy.[33]

Electroencephalography

Specific electroencephalographic changes associated with various types of clinical seizures are reviewed extensively elsewhere.[20, 21, 23, 24] The electroencephalographic patterns in childhood are more variable and at the same time of greater prognostic value than are those in adults. Routine recordings should be supplemented by activation technics or localization studies to substantiate the diagnosis of a convulsive disorder and to evoke a specific or focal dysrhythmia. Refined methods of cerebral localization are particularly important if the patient has attacks which indicate a focal origin.[20, 41]

In 1924 Foerster[34] demonstrated that epileptic attacks are sometimes elicited by hyperventilation, and Lennox[35] used this technic to confirm the diagnosis of petit mal before the introduction of electroencephalography. Alterations in the electrical activity of the brain during overventilation, which consist of an increase in the amplitude of the discharges and a decrease in their frequency, are dependent on lowering the carbon dioxide content of the blood. These changes, termed "build-up," are observed more often in children than in adults.[36] They occur in the most extreme form in children with seizures belonging to the petit mal triad; in this group the specific spike and wave electroencephalographic dysrhythmia and clinical attacks may occur in response to hyperventilation.

Sustained antidiuresis, produced by the injection of PITRESSIN® and forced water drinking, has been used since 1931 to induce convulsions as a diagnostic test.[37] Recently this method has been employed to evoke suspected electroencephalographic changes,[38, 39] although the results are not highly specific for convulsive disorders.[40] The slow intravenous injection of METRAZOL® during recording may reveal latent electroencephalographic abnormalities;[41, 42] however, it may not be successful as a means of localization.[43] An extremely useful method of activation, particularly in children, is that of recording during spontaneous or sedative-induced sleep.[21] Seizure discharges which are not apparent on the waking record may be elicited during light sleep, particularly the focal electroencephalographic dysrhythmias which originate from the temporal lobe.[21]

Even during successful treatment the electroencephalogram should be repeated at least once a year; it can also be used as an aid to determine when medication can be withdrawn. If a patient previously under adequate therapeutic control again begins to exhibit seizures, additional recordings may reveal new changes in the electroencephalogram which require specific alterations in medication. A noteworthy example is the appearance of an

TABLE 1

FIRST APPROXIMATION TO ANTICONVULSANT THERAPY*

SEIZURE TYPE		DRUG THERAPY
Clinical	*Electroencephalographic*	*First Approximation*
Grand mal	Grand mal[1]	Dilantin, mesantoin, phenurone, phenobarbital, mebaral
Psychomotor	Psychomotor[2]	Phenurone, dilantin. Mesantoin or tridione may also be needed
Petit mal triad	Petit mal[3, 4]	Tridione, paradione, phenurone. Occasionally dexedrine, ephedrine, caffeine. The addition of dilantin or mesantoin may help refractory patients, especially adults
Petit mal, occasionally grand mal	Petit mal	Tridione or paradione alone, if no prior grand mal therapy
Petit mal, grand mal	Petit mal, slow wave[5]	Tridione or paradione plus grand mal therapy
Grand mal	Slow wave (not petit mal)	Dilantin plus tridione
Autonomic	Normal or random slow waves	Dexedrine or possibly phenobarbital

*Modified from Goodman, L. S. and Toman, J. E. P.: Proc. First Nat. Medicinal Chemistry Symposium. Am. Chem. Soc., June 17-19, 1948, pp. 93-113.

1. Spike or sharp waves.
2. Sleep record—focal intermittent spikes, anterior part of temporal lobe. (Gibbs, F. A., Gibbs, E. L. and Fuster, B.: Anterior temporal localization of sleep-induced seizure discharges of psychomotor type. Tr. Am. Neurol. A. 72:180, 1947).
3. 3/sec. spike wave.
4. Sleep record may show "status pyknolepsy."
5. More characteristic interseizure record, especially in children and young adults.

unsuspected dysrhythmia of the petit mal or petit mal variant type.

Therapy

Various methods have been used in the past for controlling convulsive disturbances, including starvation,[45] restriction of fluid or salt intake[46] and the production of ketosis by means of the ketogenic diet.[47, 48, 53] Moderate fluid restriction is still considered a useful adjunct to anticonvulsant medication, and some clinicians still prefer the ketogenic diet to drug therapy for children[49, 52, 53] despite its cost and the difficulty of its management. Its effective use depends on the maintenance of a high degree of ketosis by the ingestion of large amounts of fats with a relatively low intake of carbohydrates and proteins. A detailed account of dietary management, including menus, can be found in the publications of Peterman[50] and McQuarrie.[51]

The first anticonvulsants were principally sedative; the bromides were introduced by Locock in 1857[54] and phenobarbital by Hauptman in 1912.[55] Divorce of the anticonvulsant from the sedative effects took place with the introduction of DILANTIN® by Merritt and Putnam in 1938.[56] Since that time, continuous research has added a number of useful agents to our armamentarium. Present day treatment is based on accurate clinical and electroencephalographic evaluation of the patient. Specific forms of therapy, alone or in combination, are indicated according to the kind of attacks presented. Table 1 is an outline of the first approximation to therapy according to clinical seizure types and associated electroencephalographic dysrhythmias.

Grand mal and focal cortical seizures (not including the psychomotor group) respond favorably to the barbiturates (phenobarbital and MEBARAL®) and to the hydantoins (dilantin and MESANTOIN®). Patients with psychomotor attacks do not respond as well as those with grand mal epilepsy to the barbiturates but may benefit from the use of dilantin, mesantoin or PHENURONE®.

Phenobarbital is the least toxic of the

agents listed and remains the drug of choice for infants and young children. Those whose seizures occur only at night may take the full daily dose at bedtime. Mebaral is the only other member of the barbiturate series with specific anticonvulsant properties.[57] It is considered by some clinicians to be less sedative and, therefore, preferable to phenobarbital.[58]

Dilantin is now available in the form of a scored, flavored tablet containing 0.05 gm., which will be useful for small children who fail to respond to the barbiturates. A child of school age, if given phenobarbital alone, will usually find the effective dose too soporific, so that dilantin, alone or combined with a small dose of phenobarbital, is indicated. The toxic effects of dilantin consist of diplopia, nystagmus, ataxia, headache, apathy, increased irritability and drowsiness or insomnia. An erythematous, scarlatiniform or morbilliform rash may occur, often accompanied by fever and leukocytosis; severe forms of dermatitis are quite rare.[59] Unpleasant side effects consist of hyperplasia of the gums, gastrointestinal irritation and hirsutism. Because of its extreme alkalinity, dilantin is not suitable for parenteral administration. It is of no value in treating emergency conditions such as status epilepticus.

Mesantoin is useful alone or combined with dilantin in the treatment of refractory grand mal and psychomotor epilepsy. Clinical toxicity includes oversedation which usually precludes the combination of mesantoin with the barbiturates. A rash may occur in 6 to 15 per cent of patients receiving mesantoin,[60,61] but may be averted by the use of small doses of the drug during initial therapy. Skin eruptions may be accompanied by changes in the blood. Bone marrow depression may be encountered as long as months or years after the start of medication. Patients should be warned to report such symptoms as weakness, pallor, sore throat or unusual bleeding. Blood studies should be made at least once a month and mesantoin should be discontinued if progressive anemia is apparent, if the number of neutrophils is decreasing or if the platelets are reduced or absent.

The therapeutic effects of thiantoin are similar to those of dilantin; however, it has recently been withdrawn from the market because of reports of pancytopenia and toxic hepatitis.[62-64]

Phenurone is particularly effective in psychomotor epilepsy and in the management of refractory or mixed types of seizures.[65,66,68] In the latter group, the addition of small doses of phenurone to other therapeutic agents may be helpful. Because of possible toxic reactions, phenurone should be reserved until other combinations have been found to have insufficient effect. Untoward effects include anorexia, disturbances of sleep, rash, headache, toxic hepatitis, bone marrow depression and exaggeration of personality disorders. Children, in contrast to adults, may show improvement in behavior and personality.[67] Patients receiving phenurone should be warned of possible untoward effects and should be followed closely. Monthly examinations of the blood and urine, including determination of urinary urobilinogen or other appropriate tests of liver function, are mandatory.

Tridione and paradione[69] are available for the treatment of seizures belonging to the petit mal group. Tridione may increase the frequency of grand mal seizures and should, therefore, be used in combination with phenobarbital or dilantin in children having both petit mal and grand mal. Untoward effects include irritability, gastric distress and somnolence. A generalized morbilliform rash may occur in 10 to 15 per cent of patients[69,70] and this necessitates immediate withdrawal of the drug; but in the majority of cases the rash will not reappear when the drug is reinstated after an interval of two weeks. Photophobia may be bothersome in older children and adults, but the drug has no serious effects on the eyes, and the discomfort may be relieved by the use of tinted lenses. Neutropenia occurs in 20 per cent of patients;[69] several cases of fatal pancytopenia have been reported.[71] Paradione is slightly more sedative than tridione and may prove useful in patients who are refractory to the latter. It is particularly useful in the control of akinetic seizures.[72] To date, fewer toxic reactions have been noted from paradione than from tridione.

TABLE 2

ANTICONVULSANTS GENERALLY AVAILABLE; AVERAGE DOSE RANGE IN GRAMS PER DAY

DRUG	AGE (YEARS)			
	Below 2	*2-5*	*5-10*	*Above 10*
Grand Mal, Psychomotor				
Phenobarbital Tablet: 0.016, 0.032, 0.065, 0.1 Elixir: 0.016/4 cc.*	0.032-0.048	0.032-0.065	0.065-0.1	0.1-0.3
Mebaral Tablet: 0.032, 0.065, 0.1, 0.2	0.032-0.065	0.032-0.1	0.065-0.3	0.2-0.4
Dilantin Sodium Capsule: 0.03, 0.1 Tablet: 0.05	0.05-0.1	0.1-0.2	0.2-0.3	0.3-0.4
Mesantoin Tablet: 0.1	0.1-0.2	0.2-0.3	0.3-0.4	0.4-0.6
Phenurone Tablet: 0.5	0.25-0.5	0.5-1.0	1.0-2.0	1.0-3.0
Petit Mal				
Tridione Capsule: 0.3 Dulcet: 0.15 Solution: 0.15/4 cc.*	0.3-0.45	0.45-0.9	0.6-1.5	0.9-1.5
Paradione Capsule: 0.3 Liquid Concentrate: 0.3/cc.*	0.3-0.45	0.45-0.9	0.6-1.5	0.9-1.5

*Grams per indicated number of cubic centimeters.

Amphetamine or DEXEDRINE® is of limited value, but occasionally it is effective, either alone[73] or combined with tridione, in the control of petit mal. It is specific for diencephalic or autonomic epilepsy, a variety of seizure which rarely occurs in children; the drug has also been reported to be useful in children with behavior disturbances.[74, 75] It is also valuable in counteracting the sedative effects of the anticonvulsants. Untoward reactions include restlessness, insomnia, anorexia and weight loss.

Children respond with greater individual variation to anticonvulsants and require proportionately larger doses than do adults (see Table 2). Satisfactory regulation of therapy may require frequent observation over a period of weeks or months. A safe rule is to start with the least toxic agent of choice, beginning with the smallest effective dose and gradually increasing to doses which provide maximal control or which represent the limit of tolerance. Other therapeutic agents may then be added or substituted until satisfactory results are obtained. Children with mixed types of seizures may require combined therapy, but if possible the use of two potentially toxic drugs should be avoided. Anticonvulsants should never be withdrawn except in extreme emergency, at which time provision for substitute therapy should be made. If potentially toxic drugs are to be used, the patient or his parents should be warned of the risk and told to watch for untoward symptoms.

All patients receiving anticonvulsants other than phenobarbital, mebaral and dilantin should have a blood examination at least once a month. Necessary hematologic studies include a white blood cell count, a hemoglobin or hematocrit determination, and a differential count with particular attention to the number of platelets on the blood smear. These studies should be continued as long as the patient is receiving any of the potentially

toxic agents. All patients receiving tridione or paradione should have periodic urinalyses. Those receiving phenurone should have liver function tests performed at least once a month. Anticonvulsant dosages should not be excessive, but must be adequate. As long as the attacks are well controlled, the least toxic and the least expensive form of treatment should be employed. The physician must always keep in mind that treatment will be chronic and the financial burden to the family must be given serious consideration.[71]

The physician treating recurrent seizures in children must not become preoccupied with medical supervision and overlook the child as a person. It is important to inquire into his reactions and those of his parents toward his illness, and to allay fears and misconceptions. Effort should be spent toward his acceptance in the family circle, and the extremes of overindulgence or rejection should be avoided. Acceptance among his associates and optimal adjustment in school are also essential to the total well-being of the child with seizures. Educational or vocational planning should be made as early in life as possible. Medical research has now made possible adequate seizure control in 75 per cent of epileptic patients; it is equally important that they be given every opportunity to become useful members of society.

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The Ever-Continuing Search For Immunity in Tuberculosis

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Part 3

Because of the recognized danger of introducing into human bodies living tubercle bacilli in so-called BCG cultures, revival of the use of dead organisms has occurred during the past few years. Such "vaccines" have never proved efficacious. Although the tuberculin reaction only detects presence of allergy, it continues to be used as a criterion of immunity. Accomplishments by standard methods are erroneously credited to immunizing agents. The propaganda for BCG now seriously threatens the most successful tuberculosis program of all time. Some persons are refusing sanatorium care while others leave institutions thinking their associates can be immunized. Many persons are dubious about supporting the tuberculosis Christmas Seal sale, believing the National Tuberculosis Association will soon be unnecessary. Legislators question appropriations for sanatoriums on the grounds that such institutions soon will be obsolete because of BCG. In some places much of the money so needed for case-finding and sanatorium care is being diverted to BCG programs. To date there is no incontrovertible proof that BCG or any other so-called immunizing agent has been effective in preventing or controlling tuberculosis anywhere. Whenever claims are made for its efficacy, better results are in evidence in similar areas and other nations where it has not been used.

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Use of Dead Tubercle Bacilli Revived

THE danger of introducing living tubercle bacilli into humans has long been expressed, regardless of the supposed low virulence of these bacilli. The possibility, or even probability, of mutation, regained virulence, etc., has caused much fear of any such procedure. With the recent discovery that cultures of so-called BCG contain multiple bacterial forms instead of just the original BCG and that these forms vary markedly in invasiveness of animal tissues, and with the established fact that present day BCG produces progressive and killing tuberculosis in certain animals, there is rapidly developing a revival of the use of dead tubercle bacilli by those who still believe that immunity exists in tuberculosis.

Olson, et al.[131] studied (1) virulent human type tubercle bacilli killed by ultraviolet irradiation, (2) live *Bacillus Calmette-Guérin*, (3) ultraviolet-killed *Bacillus Calmette-Guérin* and (4) heat-killed virulent human type tubercle bacilli. The ultraviolet-killed, virulent tubercle bacilli, in three doses, produced resistance equal to that of a single dose of living BCG and was more effective in guinea pigs than three doses of living BCG against massive doses of virulent tubercle bacilli. The virulent strain killed by ultraviolet light made a more effective "vaccine" against this strain than did the same virulent strain killed by heat or the BCG killed by ultraviolet light.

Sarber, et al.[132] produced irradiated vac-

cine by killing virulent human type tubercle bacilli with ultraviolet light. Another vaccine was prepared in the same manner from *Bacillus Calmette-Guérin*. These vaccines were introduced into different groups of animals. Three weeks after the last dose, virulent tubercle bacilli were administered to both vaccinated groups and controls. All animals which died prior to four months following the procedure were carefully examined for presence and extent of tuberculosis and cause of death, such as intercurrent infection. Those which survived for four months were killed and the gross tuberculous lesions found at autopsy were recorded. These workers conducted several other similar experiments and found that ultraviolet-irradiated, virulent human strain of tubercle bacilli had antigenic value at least equal to living BCG on the basis of guinea pig "protection" tests.

Paterson, et al.[133] administered dead vole tubercle bacilli to 50 guinea pigs. Another 50 received living BCG, and 50 others were used as controls. These authors found that the degree of "protection" afforded by killed vole bacilli was comparable to that obtained from live BCG. Moreover, the efficacy of dead vole bacilli was as great as that reported by others who had used live vole bacilli. These authors stated that "the advantages of a vaccine made from dead organisms only are obvious."

Aoyama[133a] (Japan) opposes the use of living tubercle bacilli such as BCG, but recommends A-0, which is made from killed human type S-form bacilli of various strains.

Petragnini's anatuberculin has been used extensively as a vaccine in Italy. It consists of dead tubercle bacilli. Ferro, et al.[133b] reported that in an epidemic of tuberculosis among institutionalized babies, 9 of the 54 who had received this vaccine developed enlargement of hilum structures within one year, while 9 of the 78 unvaccinated babies developed hilum changes and 12 had miliary, meningitic and progressive pulmonary disease, of whom 11 died.

No Dependable Criterion of Immunity

Wherever tuberculosis was prevalent, it had long been observed that tuberculous lesions containing deposits of calcium and/or fibrous tissue were present in the bodies of many persons who had died as a result of nontuberculous conditions. It was postulated that the infection had resulted in immunity responsible for controlling the lesions. In the bodies of other persons, in addition to these calcified and fibrous lesions, there were progressive areas of disease which had not been responsible for illness or death of the individual. It was thought that such persons had received massive doses of bacilli with which immunity had not yet been able to cope. In still other bodies, in addition to calcified and fibrous lesions, there was progressive disease which had caused death. This was believed due to overwhelming infections which had broken down immunity and caused death before adequate immunity could be re-established.

With the advent of roentgenographic inspection of the chest, shadows of lesions nearly always thought to represent tuberculosis were observed on the films of some persons apparently in excellent health. Often shadows suggested the presence of calcification and fibrosis. Thus it was deduced that immunity had brought the lesions under control and that further infections or lesions would not develop. However, careful and lengthy observations of apparently healthy tuberculin reactors and of those with innocent-appearing, shadow-casting lesions rendered previous theories about dependable immunity obsolete.

Tubercle bacilli often stimulate the proliferation of connective tissue cells and, in many cases, small to large amounts of fibrous tissue are deposited. This is a response to an irritant and cannot be considered due to specific immunity, since other irritants (notably silicon dioxide) result in as much or more fibrosis.

It was long thought that depositions of calcium salts seen at necropsy and in roentgenographic shadows were diagnostic of tuberculous lesions. They were usually spoken of as representing healed areas of disease and thus were said to indicate that the body had developed satisfactory immunity. It is now

known that deposition of calcium salts is not specific for any disease but may occur wherever there is caseation or pent-up pus, regardless of cause. Therefore the presence of calcium deposits in the dead or living lung by no means indicates that the original lesion was caused by tubercle bacilli. In some areas of this country it is now known that fungous infections result in more calcium deposits in the chest than do tubercle bacilli.

In the bodies of persons who have died from tuberculosis, in addition to the killing disease there are lesions apparently of long standing, calcified and/or fibrosed. If these lesions result in dependable immunity, why do nearly all persons who die from tuberculosis have them? Why is this disease, of such antiquity at the middle of the twentieth century, the first cause of incapacity and death of all diseases among the people of the world? If everyone had an attack of smallpox prior to the age of 18 years, there would be practically no illness or death from this disease among adults. Yet in areas of the world where practically everyone has had an attack of tuberculosis prior to the age of 18 years, clinical tuberculosis exists almost in epidemic form, incapacitating and killing huge numbers of adults beyond that age. In this country tuberculosis is often spoken of as a disease of old people. Mortality rates reach their greatest height among persons 70 years of age and older. In many places more than 50 per cent of deaths from tuberculosis occur among persons 50 years of age or over. Much of this destruction among elderly people is the result of infections acquired in childhood. Medlar, et al.[134] have referred to tuberculosis in old age as the disregarded seedbed of the tubercle bacillus. If dependable immunity had resulted from primary infections earlier in life this situation would not obtain.

Clinical tuberculosis is notoriously a relapsing disease; it can never be classified as cured in the strict sense of the word. If one follows those persons who present roentgenographic shadows and other evidence of stable tuberculosis lesions for a sufficiently long period of time, many lesions will be seen months and years later to have become progressive and new ones will have appeared.

In tuberculosis there is nothing concerning which less is known than immunity. There is no criterion to determine how much, how little or whether any is present in an individual case. All that is known with certainty is that dependable immunity has never been demonstrated in humans.

Tuberculin Reaction Not a Criterion of Immunity

After tuberculin became available in 1890, Ghon (1916) demonstrated that all tuberculin reactors have tuberculous lesions. Among the large numbers of persons found to react to tuberculin in some parts of the world, the majority appeared to be in excellent health at the moment, and conventional physical examinations yielded no evidence of disease. Therefore it was assumed that such persons were immunized and the tuberculin reaction was regarded as a safe criterion of the presence of dependable immunity.

Earlier in this century it was known that when children first became infected with tubercle bacilli a small percentage had erythema nodosum, pleurisy, enlargement of hilum structures and small pulmonary infiltrates. These were in evidence at about the time allergy could first be detected by the tuberculin test. The occasional child had considerable fever, usually lasting from one to several weeks. When these manifestations subsided the children appeared well and thereafter were thought to be immunized.

The majority did not have such symptoms or findings. They only reacted to tuberculin. Soon after allergy was established, the occasional one would have an acute, fatal reinfection form of tuberculosis, such as pneumonia, meningitis or miliary disease. During the next few years, some would develop extrathoracic tuberculosis in such organs as lymph nodes, kidneys, bones and joints. With the appearance of puberty the occasional one developed chronic clinical pulmonary tuberculosis. Largely because so few presented these reinfection forms of tuberculosis in any one year after allergy appeared, little attention was called to them, and all the others were thought

to be immunized. Thus a firm belief was established that sensitivity to tuberculoprotein indicates immunity to tuberculosis. The erroneousness of such thinking was not realized until groups of children were observed well into adulthood, when it was seen that most of the illness, incapacity and death occurred among those who had been "healthy" tuberculin reactors for some time.[135]

During the first decade or so of this century it was believed that most children became infected with tubercle bacilli by the age of 15 years. The tubercle bacillus was thought to be ubiquitous. When isolation of tuberculous patients got under way and tuberculosis was being brought under control in cattle, it was observed that many children were passing into adulthood without tuberculous infection. Prior to this, numerous teen-age girls and boys were seen to fall ill from tuberculosis and many died. Although no one had made actual observations, the theory was advanced that it was the teen-age girls and boys who were receiving first infections in adulthood who were dying promptly because of lack of immunity. Thus theorists expressed alarm, as they were convinced that such persons were headed for destruction. In fact, pressure was exerted to find those children and young adults who did not react to tuberculin and sensitize their tissues to tuberculoprotein by producing tuberculous lesions in them with BCG. *We could see no premise for such a procedure.* It already had been established that natural infection with virulent tubercle bacilli does not produce dependable immunity or resistance against later attacks of clinical disease. Thus it could hardly be expected that an organism of low virulence would do so. Moreover, we sought to avoid tuberculous lesions rather than produce them, even with an organism said to have low virulence. Furthermore it had been established that destructive forms of clinical tuberculosis, both acute and chronic, usually develop in tuberculin reactors.

As the years passed, we had the opportunity to determine the validity of the belief that infections acquired first in adulthood are likely to result promptly in rapidly progressive tuberculosis. We observed many young adults, particularly students of nursing and medicine, who acquired primary tuberculosis.[102, 103] These individuals exhibited the same defense mechanism against the first invasion with tubercle bacilli that we had seen in so many children. There was no essential difference between primary tuberculous lesions of young adults and those of children. Rapidly progressive tuberculosis did not develop more often among the primarily infected adults than among children.[136] As time passed we observed that older persons who became primarily infected responded just as children and young adults. Therefore, the theory so long extant—to the effect that primary tuberculosis is more dangerous in adulthood than in childhood—proved to be a myth among the individuals of the groups under our observation.

Rich[137] made an intensive study of this subject and concluded that there is no law of parallelism between hypersensitivity and acquired resistance in tuberculosis. With reference to BCG, Dubos[114] said:

> The development of a positive tuberculin test is universally used as a criterion that the vaccine has "taken" but, unfortunately, as already pointed out, the relation of tuberculin allergy to immunity is one of the most obscure aspects of the pathogenesis of tuberculosis. . . . A test devised to measure streptococcal allergy does not measure resistance to streptococcus infection and by analogy the tuberculin test does not necessarily reflect immunity in tuberculosis.

Statements so often heard that 95 per cent of 50,000 or any other number of children who received BCG were successfully vaccinated are exceedingly misleading. To most persons, professional and otherwise, the phrase "successful vaccination" means the establishment of immunity. In this case, however, it only means that 95 per cent of the total number have had their tissues sensitized to tuberculoprotein by reason of tuberculous lesions produced in their bodies by BCG.

Xalabarder[137a] states that the present day tendency of applying BCG vaccine transcutaneously has only the purpose to obtain the tuberculin reversal in the greatest proportional number of cases. However, very little is known about the helpful or harmful char-

acter of a positive cutireaction so obtained for the spontaneous evolution of tuberculosis.

Since the tuberculin reaction has never been proved to be anything more than a test for allergy to tuberculoprotein, there is no basis for using it as a criterion of immunity.

Tuberculin Reaction Only Denotes Presence of Allergy

Before the first invasion with tubercle bacilli, the tissues of humans and animals are not allergic to tuberculoprotein. Hence this protein is harmless to them. It can be injected into tissues, dropped into the eyes or swallowed in concentrated form without causing harm or reaction. Thus when tubercle bacilli first invade nonallergic tissues no specific reaction occurs. The body's defense mechanism goes to work as with other foreign material, including particles of silicon dioxide.

Lemon and Feldman[138] found that for some time after invasion of tissues with tubercle bacilli and silica particles it is impossible to distinguish morphologically between developing tubercles and silicotic nodules. Tubercle bacilli become partially encapsulated in the absence of allergy. By the time allergy develops to such a degree that it can be elicited by the tuberculin reaction (three to seven weeks after the invasion) tubercles have resulted in only slight destruction of tissues. Thus primary tuberculosis per se is usually an exceedingly benign disease.

The development of sensitivity of tissues to tuberculoprotein, however, is the setting of the stage for all the destruction from exogenous or endogenous reinfections which tubercle bacilli are capable of causing. Krause[139] has written:

> Accordingly the allergic reaction is seen to be responsible for all of the acute manifestations of tuberculosis and, when so considered, it must be viewed as a potent contributor to pathogenesis. Human beings pass as perfectly well as long as they hold their tuberculous infections asymptomatic, inactive. But they are allergic and any discharge of sufficient focal material to a new place will render them immediately ill because of the allergic reaction that ensues promptly.

Concerning native African boys, Cummins[139a] said:

> The high degree of allergic hypersensitivity in these African mine recruits is remarkable and the more hypersensitive they are to tuberculin, the more liable are they to break down into acute tuberculosis.

Usually the human body defends itself well against the first invasion with tubercle bacilli regardless of the age in life when it occurs. For example, when 1000 persons of all ages are infected for the first time, a few may have such symptoms as fever, malaise, erythema nodosum and accelerated erythrocyte sedimentation velocity for a short time. None dies. However, when the same 1000 persons are reinfected exogenously or endogenously after the tissues become allergic one may expect both acute and chronic forms of clinical tuberculosis to appear in a considerable number during the remainder of their lives. Acute forms of reinfection type of tuberculosis, such as meningitis, miliary disease and pneumonia, may develop soon after allergy is well established, and for this reason such conditions were long erroneously thought to be primary.

Allergy to tuberculoprotein causes reinfections with tubercle bacilli to be so much more destructive than primary lesions because tuberculoprotein is a deadly poison to allergic tissues.

Seibert[140] sensitized normal guinea pigs with tuberculin (tuberculoprotein) but these animals demonstrated no immunity or increased resistance to tubercle bacilli. On the contrary, she said:

> It seems to hasten and extend the lesions and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals.

In studying tissue cultures, Holst,[141] Stewart, Long and Bradley[142] found that leukocytes from animals whose tissues were not allergic to tuberculoprotein were not harmed when brought in contact with tuberculin, whereas leukocytes from allergic animals were definitely damaged under the same treatment. Rich and Lewis[143] exposed washed cells of normal and of allergic guinea pigs to measured amounts of tuberculin. They used several hundred cultures of white blood cells and of spleen and observed that the cells obtained from tuberculous animals were killed by amounts of tuberculin in which cells

from nonallergic animals grew freely. Aronson[144] reported that tuberculin made from mammalian types of tubercle bacilli inhibits growth of cells from explants of bone marrow, spleen and testes of tuberculous guinea pigs and is toxic for these cells, but has no effect on explants of the same tissues from nontuberculous animals.

When tubercle bacilli invade allergic tissues and begin to liberate protein, there is a much greater response of the white blood cells than there was to the primary invasion. The reaction is specific. Thus, tubercle bacilli are fixed at the site of the invasion for the time being.

Krause[145] introduced tubercle bacilli subcutaneously in the groins of nonallergic guinea pigs and found that some bacilli traveled to the lungs, tracheobronchial lymph nodes and spleen in four days or less. These animals died from tuberculosis in approximately three months. The same experiment conducted with a group of allergic guinea pigs showed that bacilli did not reach the lungs, tracheobronchial lymph nodes and spleen until three weeks to 30 days later, and these animals did not die from tuberculosis until 10 to 11 months later. It was the temporary fixing power of the tissues due to allergy which delayed tubercle bacilli in the allergic animals. However, bacilli reached the same destination and killed just as certainly as those introduced into the bodies of nonallergic animals.

On first thought the prompt fixing of tubercle bacilli at their sites of lodgment seems to be a desirable situation, but subsequent developments often prove it to be otherwise. The defense mechanism usually is not capable of destroying all tubercle bacilli; therefore, from these fixed colonies more tuberculoprotein is produced and liberated, thus killing more cells and tissues. When these lesions are in the lungs, the necrotic tissue may be evacuated by way of bronchial ramifications, and pulmonary cavities remain.

In the numerous preparations of living and dead tubercle bacilli used as vaccines since 1882, it was allergy which falsely gave so much temporary encouragement and spurred physicians and scientists on unceasingly with the hope of producing an efficacious immunizing agent against tuberculosis in animals and man. Thus the tuberculin reaction is a test for allergy which is a prerequisite to the development of destructive and killing forms of tuberculosis.

Factors Which Result in Erroneous Conclusions

In practically every attempt to immunize people against tuberculosis, numerous factors have resulted in misinterpretations:

1. Regarding the tuberculin reaction as evidence of immunity.
2. Protecting the vaccinated against exposure and leaving controls in contact with contagious cases.
3. Administering BCG to children of intelligent and cooperative parents and using other children as controls.
4. Selecting subjects on family group basis.
5. Comparing morbidity and mortality rates among those who have received BCG with those of similar groups before the BCG projects were instituted.
6. Comparing unlike conditions such as allergic manifestations (e.g., erythema nodosum), with significant clinical lesions.
7. Drawing conclusions from insufficient periods of observation.

To administer BCG to children and draw conclusions as to efficacy within 5, 10 or 15 years is unsound. Even at the end of 15 years these children are just reaching the age when clinical tuberculosis begins to enter its most destructive phase. Therefore, only through many decades of observation of such individuals could it be possible to determine the efficacy of any so-called immunizing agent.

Observations on persons with natural tuberculous infections provide an excellent lesson. In the past, children who had been in intimate contact with tuberculous parents and who appeared well long after death of their parents were thought to have become immune, but when an opportunity came to follow them through second and third decades of life, and even later, enough of them fell ill from clinical tuberculosis to give the medical observer no

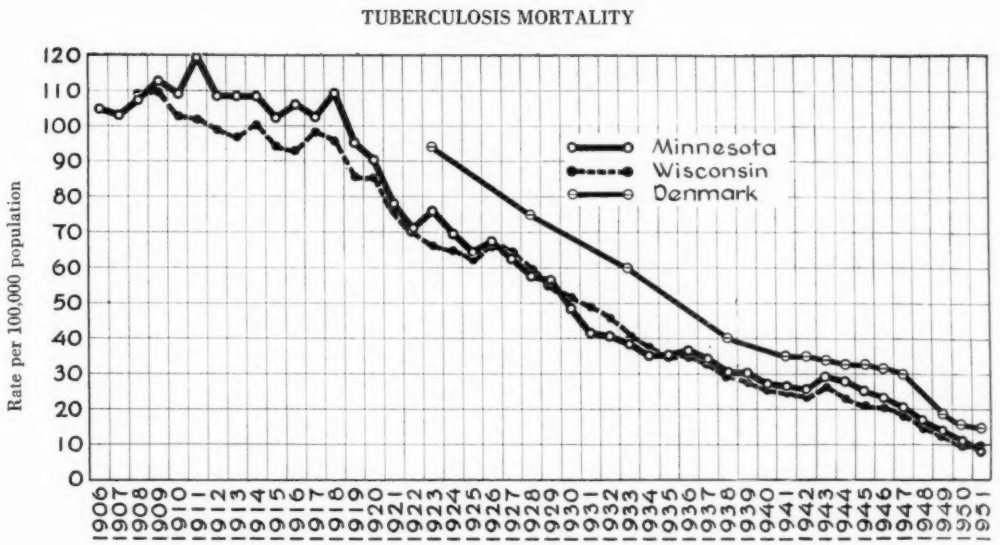


FIGURE 5. Tuberculosis mortality curves for Denmark, Wisconsin and Minnesota—areas which have approximately the same size populations. These areas have had effective fundamental tuberculosis control programs consisting of case-finding, isolation of patients with contagious cases, etc. In 1927 Denmark began to employ BCG for children and adults living in tuberculous surroundings. Between 1940 and 1944 the BCG program was increased to such an extent that practically all school children between the ages of 10 and 14 years were ultimately vaccinated. In Wisconsin and Minnesota BCG has been administered to an insignificant number of persons. The Danish graph does not reveal any significant decline in mortality during the period that BCG has been in use that cannot be accounted for by the fundamental program. If BCG were efficacious the mortality rate in Denmark should have dropped much more precipitously than that in Wisconsin or Minnesota. Obviously, if any substance—even normal saline solution—had been injected into all children in Denmark, Wisconsin or Minnesota since 1920, significant claims might now be made erroneously for its efficacy. Nevertheless Denmark is the area so often referred to as having made significant accomplishments with BCG.

confidence in the presence of dependable immunity.[135] When tuberculin became available the same long interval between the development of sensitivity to tuberculoprotein and the appearance of most chronic clinical disease deceived physicians everywhere. Large numbers of tuberculin reactors looked healthy. They presented no significant roentgenographic shadow-casting lesions. Only when physicians had the opportunity to re-examine such individuals periodically over a few decades did the truth come to light.

We reported a study of 813 children who reacted to tuberculin between birth and 5 years of age. Only 11 (1.35 per cent) died from tuberculosis in childhood; 11 others developed extrathoracic lesions which were treated successfully. The remaining 791 (97.3 per cent) presented no evidence of clinical disease during childhood. It might have been argued that these 791 children were immunized had the period of observation been terminated when adolescence was attained. Our studies have revealed that among adult tuberculin reactors the incidence of clinical tuberculosis increases with the duration of the period of observation.[135a]

Levine and Sackett[94] have called attention to numerous factors involved in the reduction of tuberculosis, all of which must be properly evaluated. The use of BCG in areas where the disease is decreasing as the result of other factors already in operation should result in a much more rapid decrease if the claims for its efficacy are true. To date such a report has not been forthcoming (Figure 5).

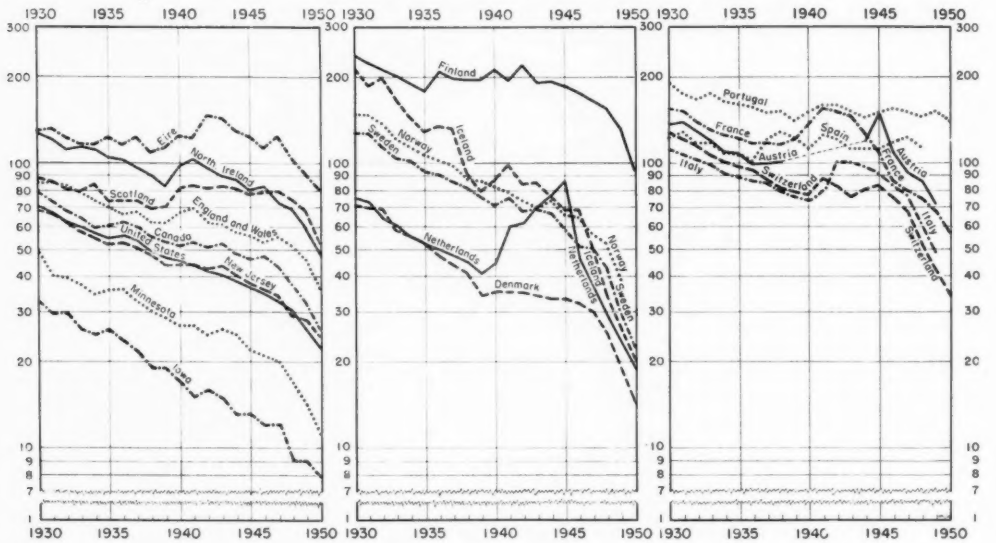
Accomplishments by Standard Methods Credited to Immunizing Agents

During the past two decades considerable

TUBERCULOSIS DEATH RATE*

(SINCE 1930)

United States, states of New Jersey, Minnesota and Iowa, Canada, England and Wales, Scotland, Northern Ireland, Eire, Iceland, Finland, Sweden, Norway, Denmark, Netherlands, France, Switzerland, Austria, Italy, Spain, Portugal



*Per 100,000 population.

FIGURE 6. Note the marked downward trend in tuberculosis mortality in several nations and states in the past few years. The decrease is as marked, or more so, in places where BCG has not been used. The rather precipitous decline since 1945 in most of the areas included in these graphs is thought to be due largely to bacteriostatic drugs, particularly streptomycin and para-aminosalicylic acid, which have at least postponed many deaths from tuberculosis. Another important factor, particularly in the Scandinavian countries, has been the accelerated campaigns against bovine tuberculosis during the past decade. Mass x-ray and other surveys apparently have also played a significant role in finding cases; also, these patients have been isolated and treated at a time when the best results could be expected from these procedures. These graphs do not reveal evidence that BCG has played a significant part in any area. (From Drolet and Lowell.[152])

TUBERCULOSIS MORTALITY RATE

United States

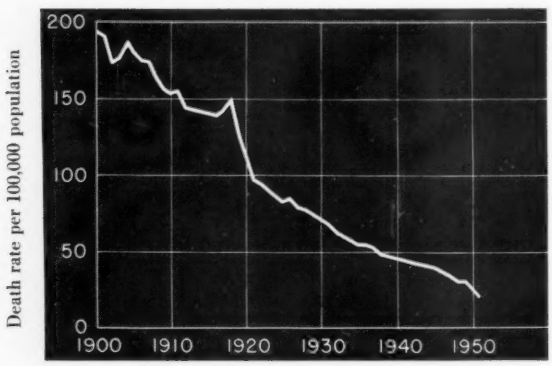
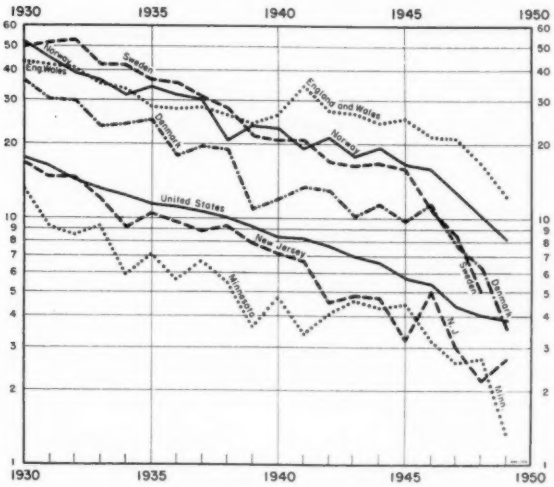


FIGURE 7. Note the precipitous decline in tuberculosis mortality which occurred in the United States earlier in this century. This is thought to have been due largely to the extensive educational campaign, the control of tuberculosis in animals, and to the provision of hospitals and sanatoriums for the isolation of contagious cases. With these procedures in continuous operation, the mortality rate has rapidly decreased to 19.6 per 100,000 population in 1951 without the use of BCG. This is the lowest rate of any nation of 10,000,000 population. Moreover, states with population sizes the same as those of smaller nations have definitely lower mortality rates than those of such countries where BCG has been employed. (From Drolet and Lowell.[152])

TUBERCULOSIS DEATH RATE*

(CHILDREN UNDER 15, SINCE 1930)

United States, states of New Jersey, Minnesota, England and Wales, Norway, Sweden, Denmark

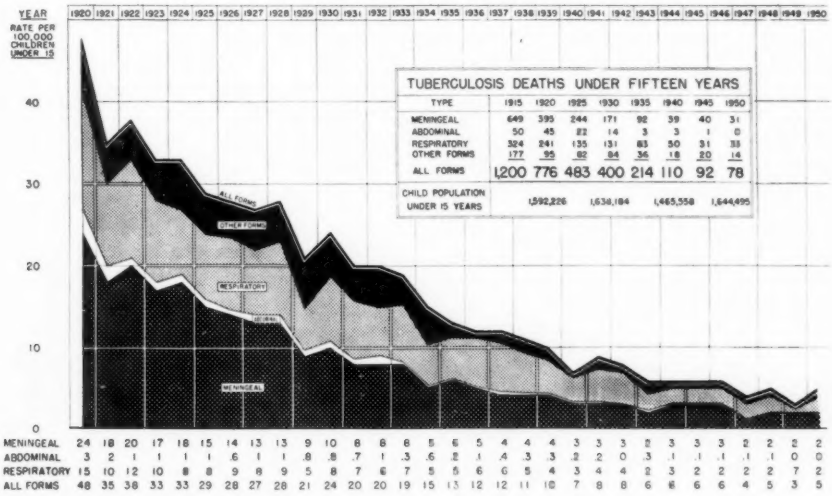


*Per 100,000 children under 15 years of age.

FIGURE 8. Since BCG was first administered to infants and children, one would expect the lowest mortality rates to obtain in this age group. The mortality rate graphs, however, show as precipitous declines in areas where BCG has not been employed as in areas with populations of corresponding sizes where it has been used extensively. (From Drolet and Lowell.[152])

TUBERCULOSIS DEATH RATE, NEW YORK CITY

(CHILDREN UNDER 15)



TUBERCULOSIS DEATHS UNDER FIFTEEN YEARS

TYPE	1915	1920	1925	1930	1935	1940	1945	1950
MENINGEAL	649	395	244	171	92	39	40	31
ABDOMINAL	50	45	22	14	3	3	1	0
RESPIRATORY	324	241	135	131	83	50	31	33
OTHER FORMS	177	95	82	84	36	18	20	14
ALL FORMS	1,200	776	483	400	214	110	92	78
CHILD POPULATION UNDER 15 YEARS		1,592,226		1,638,184		1,465,558		1,644,495

	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950
MENINGEAL	24	18	20	17	18	15	14	13	13	9	10	8	8	8	5	6	5	4	4	4	3	3	3	2	3	3	3	2	2	2	2
ABDOMINAL	3	2	1	1	1	1	.6	1	1	.8	.8	.7	1	.3	.6	.2	.1	.4	.3	.3	.2	.2	0	.3	.1	.1	.1	.1	.1	0	0
RESPIRATORY	15	10	12	10	8	8	9	8	9	5	8	7	6	7	5	5	6	6	5	4	3	4	4	2	3	2	2	2	2	7	2
ALL FORMS	48	35	38	33	33	29	28	27	28	21	24	20	20	19	15	13	12	12	11	10	7	8	8	6	6	6	6	4	5	3	5

Based on Reports, Bureau of Records and Statistics, Department of Health, City of New York.

G. J. Drolet, Statistician, New York Tuberculosis and Health Association, Inc.

FIGURE 9. The most phenomenal decline in tuberculosis mortality among children yet recorded. New York City is a highly congested area of almost 8 million people, including the Negro population of 750,000. With 1½ million children, the mortality rate decreased from 48 per 100,000 in 1920 to 3 per 100,000 in 1949, and back to 5 in 1950. Approximately one-half of the deaths among New York City children occur among the Negroes. BCG has not been used in this city except for a small study which revealed no significant efficacy. (Courtesy Drolet and Lowell, New York Tuberculosis and Health Association.)

enthusiasm for BCG was manifested in a few areas and it was given extensively, its administration even becoming obligatory for certain segments of populations. Decreasing mortality rates were observed, and proponents became so enthused that they made sweeping statements concerning the efficacy of BCG. In some of these areas—including Denmark, where BCG administration began in 1927—proponents apparently neglected to observe that the decline in tuberculosis mortality rates was no greater than that which had been occurring for some time before the BCG program was started. Indeed, there was no evidence that the mortality rates had been influenced by BCG. From the graph (Figure 5) one can only deduce that Denmark's fine fundamental tuberculosis control program plus factors which are not understood were solely responsible for the decline in mortality both before and during the BCG era. Moreover, proponents apparently neglected to observe that in other parts of the world with comparable or even larger populations where good fundamental tuberculosis programs were in operation but BCG was not used, the decline in tuberculosis mortality was as rapid and in some places more so than in Denmark (Figures 5, 6, 8 and 9). Obviously BCG was credited with that which belonged to the fundamental tuberculosis control program.

Torning [145a] (Copenhagen, 1952) says:

> The steep drop in mortality in Copenhagen in the last two years no doubt is due to a considerable extent to the fact that drug treatment has postponed but not averted a fatal issue in many desperate cases.

Burns[145b] said:

> The epidemiologist has unfortunately never been assigned the important role in the tuberculosis control program which should be his. The factors limiting his usefulness in this field have been many and varied from time to time, and have usually been due to the introduction of "panaceas" (short-cut methods of examination, immunizing agents, etc., etc.), which promised to solve quickly the entire problem without the laborious work of epidemiologists and other fundamental procedures. Such "panaceas" have always retarded progress in every phase of tuberculosis control. Now with decreasing mortality, morbidity and infection attack rates that can mean the complete control of tuberculosis in America and eradication in some areas within the life span of many of us, we are still being offered "panaceas" as promiscuously as when tuberculosis was of epidemic proportions and when it constituted a major cause of death. . . . It is apparent that by introducing "panaceas" at any point on a declining graph they may be erroneously interpreted in the future and their use justified by the still further decline of the death rate on the extended graph due to other factors.

In Japan, General Sams[146] stated that tuberculosis mortality dropped from 280 per 100,000 population in 1945 to 181.1 per 100,000 in 1948. J. Rodriguez Pastor[147] pointed out that in Japan the tuberculosis mortality rate had been rising since 1932 until it reached a peak of 280 in 1945. By 1948 this rate had dropped to 181. The analysis of deaths by ages, according to General Sams, showed that the whole reduction occurred in the immunized age group, where the mortality decreased 88 per cent. General Sams apparently has attributed this decrease almost entirely to BCG, as he says: "The BCG immunization program will in the future prevent the occurrence of most of the cases of clinical tuberculosis." Although BCG had been administered on a fairly large scale since 1944, the intense vaccination campaign under the auspices of the American Forces of Occupation did not begin until September 1946. The great decrease in tuberculosis mortality occurred in 1947, when it was reduced from 260 to 189 per 100,000. With the tremendous amount of BCG administered in 1947 and 1948, it might be expected that an even greater reduction would have occurred in 1948 if the decrease in 1947 had been due to vaccination. However, the actual reduction in 1948 was only from 189 to 181. That the marked reduction in 1947 was due to BCG seems fantastic for several reasons, including the brief time interval.

From the general health program alone, directed by General Sams between 1945 and 1948, one might expect a marked decrease in tuberculosis mortality. In fact, the general mortality rate from all causes decreased from 29.2 per 100,000 population in 1945 to 11.9 per 100,000 in 1948, a decrease of 59 per cent in three years. The factors that resulted in this decrease in general mortality could hardly be regarded as unimportant in the decrease of the tuberculosis death rate. Moreover, special fundamental work was done in

tuberculosis control during those years. By 1945, hospitals for the tuberculous in Japan had been destroyed or had ceased to function. Between then and 1949 the American Forces of Occupation had established 143 sanatoriums and also had made available for tuberculous patients a sizeable number of beds in general hospitals. General Sams' conclusions would be convincing if these other factors of long-proved efficacy had not been operating and if reductions in tuberculosis mortality had not been fully as great in other parts of the world without BCG as those in Japan.

De Abreu[148] pointed out that in Rio de Janeiro, Brazil, tuberculosis mortality dropped from 342 per 100,000 population in 1945 to 242 per 100,000 in 1948, a decrease of 29.2 per cent. This decrease occurred among those who had not received BCG, mostly in the 20 to 40 year age group, while among the children from birth to 5 years of age where BCG was employed, an increase in mortality occurred. Indeed, from 1945 to 1948 the increase was 41.3 per cent among children from birth to 1 year, 62.5 per cent among those from 1 to 2 years and 15.9 per cent among those from 2 to 4 years old. More recently de Abreu[149,150] reported that the mortality rate in Rio de Janeiro dropped from 342 per 100,000 in 1945 to 168 in 1950, a decrease of 50.9 per cent. At the same time, although BCG vaccination was intense (reaching 62 per cent of newborns in 1949), the death rate among them increased sharply.

The greatest decreases in incidence of tuberculosis and the lowest mortality rates in the world have occurred in places where BCG has not been used (Figure 6). Every favorable report made on the use of BCG can be matched by equally good or better results from areas where it has not been accepted.

David T. Smith[15] said:

> In Denmark the death rate declined from 174 in 1918 to 30 in 1947. Some BCG propagandists are inclined to attribute the decline in this Scandinavian country to the use of BCG and to ignore the effect of improved economic conditions and the standard methods of prevention. As a control for Denmark we should look at tuberculosis in Iceland. The Icelanders came originally from the Scandinavian countries and they also live in a cold climate. No BCG vaccinations have been used in Iceland and yet their death rate has dropped from 203 per 100,000 in 1929 to 26 in 1949 following the introduction of an effective control program.

M. I. Levine[95] has pointed out that in New York City, where BCG has not been used, tuberculosis mortality in children compares quite favorably with that in Gothenburg, Sweden, where practically all infants exposed to tuberculosis were given BCG but "where practically no control material was available." E. R. Levine[151] said:

> We are told that in Buenos Aires the tuberculosis death rate in children under the age of 15 years decreased some 72 per cent between 1924 and 1944. This decrease was attributed to BCG. This would appear to be convincing evidence were it not for the fact that during these same years the tuberculosis death rate in New York City decreased about 95 per cent without the use of vaccine.

No role has been played by BCG in the United States, and yet this country has the lowest mortality rate of any nation of 10,000,000 population or more (Figures 7, 8 and 9).

In the Scandinavian countries, where BCG has been extensively used, tuberculosis mortality has been decreasing, but no faster than in similar populations where BCG has not been employed.[152] The states of Wisconsin and Minnesota each have about the same population as Denmark and Norway, but without BCG their mortality rates are lower than the Scandinavian rates. In 1951 the tuberculosis mortality rate was 13 in Denmark, 9.9 in Wisconsin and 8.6 in Minnesota. Eight other states had even lower rates than Wisconsin and Minnesota (Figure 5). If normal salt solution had been extensively used under the designation "vaccine" in Wisconsin or Minnesota simultaneously with the use of BCG in Denmark, the same claim for the efficacy of such a substance might now be made in one of those states as is being made in Denmark for BCG.

Drolet and Lowell[152] said:

> During the five years from 1945 to 1950, in Norway the death rate came down from 65 to 29, or by 55 per cent; in Sweden, it fell from 59 to 22, or by as much as 63 per cent; and, in Denmark, from 33 to 14, or by 58 per cent. Against the rate of progress in these last

three countries, where BCG vaccination has been practiced on an increasing scale, must be placed the remarkable decline in the tuberculosis death rate in Iceland, whose people are of the same racial stock, and where the vaccine has hardly been utilized. In 1945, the mortality rate there was still 68 per 100,000 population; in 1950, it was 20 only, a reduction of 71 per cent—the greatest to be noted in the series of the Scandinavian countries under review.

If an immunizing agent were effective, it should first be reflected in reduced morbidity. In areas where BCG has been widely used, there is no evidence of corresponding decrease in morbidity not accounted for by other factors.[152]

Small Epidemics of Tuberculosis

Considerable fear has been expressed with reference to epidemics of tuberculosis developing in areas where the disease is being eradicated and small numbers of children and young adults have primary tuberculosis as manifested by the tuberculin reaction. Indeed, several such epidemics have been reported by Horton[152a] and by others. These will continue to occur occasionally as long as tuberculin reactors among adults are not kept under close observation to detect evolving lesions and prevent them from becoming contagious. Such epidemics are often traced to a teacher or some other person whose examinations have been neglected. These small epidemics, always resulting from neglect, are annoying, but they sink into utter insignificance when compared with places where tuberculosis is still in epidemic proportion in the entire population and remains the first cause of incapacity and death.

To experience so much fear of occasional small epidemics is an excellent indication that the areas in which they occur are on their way to eradication of the disease. These epidemics are a part of the death struggle of tuberculosis. Not long ago there was so much tuberculosis in these areas that such small epidemics were unnoticed.

To use BCG to prevent such epidemics would be another example of enthusiasm for an unproved method outrunning good judgment and wisdom. It would destroy the use of fundamental procedures which are now so successfully bringing about the eradication of tuberculosis.

Serious Threat to Tuberculosis Eradication Program

The present propaganda for BCG presents a serious threat to the most successful tuberculosis control program of all time. For nearly half a century the National Tuberculosis Association and its component organizations and practically every veterinary, nursing, medical and public health organization have developed and prosecuted an educational program against tuberculosis unequaled in the world's history. This has resulted in excellent support from legislators, victims of tuberculosis, and the general public, as manifested by the construction and operation of hospitals and sanatoriums and the patronage of those who need them. Case-finding by means of tuberculin tests, x-ray surveys and complete examinations has become popular, proving incontrovertibly the efficacy of the program. While about 200 people per 100,000 population died from tuberculosis in 1900, only 20.1 died in 1951.

In recent years, wherever an adequate number of sanatorium beds has been provided, there has resulted a decrease in demand for them, even to the point of closing some of the smaller institutions in at least one state. A recent increase[153] in the total number of cases reported to health authorities is probably explainable as follows: (1) There has been an influx of displaced persons and illegal aliens from countries where good tuberculosis control programs have never been in operation; (2) war veterans with tuberculosis are being reported at the rate of about 1000 a month, many of whom were infected and reinfected in such countries, and (3) more extensive and intensive case-finding programs have brought to light many unsuspected lesions. This does not denote an increase in the incidence of tuberculosis.

There has been a tumbling of the tuberculous infection attack rate so that a relatively small percentage of children and young adults have been infected with tubercle bacilli. Indeed, in some areas tuberculous infection has

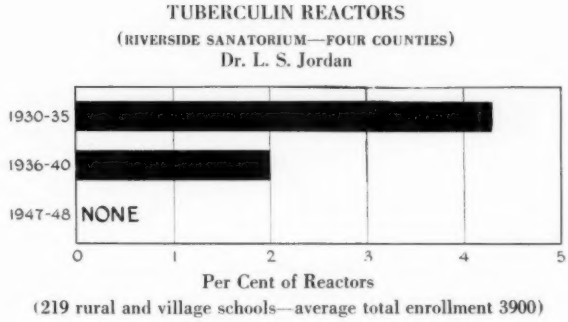


FIGURE 10. Percentage of tuberculin reactors in 219 of the 277 schools of a four county sanatorium district where an excellent tuberculosis eradication program has been pursued. By 1948 none of the 3000 children in these 219 schools reacted to tuberculin, indicating eradication of tuberculosis at this age level. No BCG was used in this area. Obviously if BCG had been employed it would have nullified the value of the tuberculin test and this fine accomplishment could not have been recognized. (From "*Invited and Conquered.*" Minnesota Tuberculosis and Health Association, St. Paul, 1949.)

been eradicated at the school age level[154] (Figure 10).

Wherever in the world this same program has been in operation sufficiently long, there has been a decrease in tuberculosis in proportion to the intensity with which the program has been executed.

The informed and cooperative public now hears on the radio, reads in magazines, etc., that a "new method" has been found to control tuberculosis safely, simply, inexpensively, quickly and effectively. This method is likened to smallpox vaccine. It is not only recommended but in some places is also obligatory for those who do not react to tuberculin. In a few places it is even advocated for both reactors and nonreactors to tuberculin.

A more conservative recommendation is that BCG be administered to all nonreactors who may be in contact with contagious tuberculosis.[155] The National Tuberculosis Association and its allies have long pointed out that anyone may be in contact with an unsuspected case of tuberculosis. Therefore every person can imagine that he is in danger of such contact and demand BCG.

Some institutions have required a tuberculin reaction for employment of personnel. Those applying for positions who do not react to tuberculin are offered BCG. Unless they accept it and become sensitized to tuberculin, they are refused employment. This procedure has not been proved to protect employees against clinical tuberculosis, but where this disease is compensable, to demand pre-employment sensitivity to tuberculin is an excellent protection for the institution against litigation when clinical disease develops among employees. However, evidence has now accrued that may cause this procedure to act as a boomerang. In the near future the courts may justifiably ask what role the tubercle bacilli introduced as BCG played in producing the clinical disease. The courts may also ask what reasoning permits artificial sensitization of tissues, when it is well known that allergy is prerequisite to the development of clinical tuberculosis.

To introduce BCG administration to institutional personnel under the guise of research is only to repeat what has already been done so many times without profit. The groups involved are too small and the observation periods too short to yield dependable information.

It is extremely doubtful whether an adequately controlled study can be conducted sufficiently long on people living in their homes to justify the effort. Nevertheless the National Research Council of Great Britain and the United States Public Health Service are attempting such studies. With such a capricious disease, decades of observation will be necessary. Concerning this, S. R. Wilson's[155a] judgment pertaining to the BCG program in Denmark also applies: "The actual result in my view cannot be assessed until one or two generations have passed and only then can it be decided whether the procedure is justified."

The impact of BCG propaganda is already reflected in a change in attitude of many people. There are those who were content to

remain in sanatoriums because of contagion but who now are seeking dismissal or leaving against advice, as they believe their children and other associates can be protected by vaccination. There are those who refuse sanatorium care for the same reason.

It has even been stated that in a few years sanatoriums will be obsolete because of vaccination. This statement has been so publicized that some legislators are said to be asking why funds should be appropriated for the building of new sanatoriums or even for repair or maintenance of those already in existence. Persons are asking, "Why buy tuberculosis Christmas Seals to support the program of the National Tuberculosis Association and its 3000 component societies, when their work will soon be rendered unnecessary through vaccination?"

Huge sums of money recently have been spent and tremendous expenditures are contemplated to propagandize nations and to send vaccination teams to administer BCG to millions. Government officials and the populace are told that they are being vaccinated against tuberculosis. They know that wherever smallpox vaccination has been practiced extensively, pesthouses for persons with this disease have vanished. They now see little or no need for a sanatorium-building program because they believe such effective vaccination is available for tuberculosis.

Marshall[155b] said:

> It is inevitable that time and money being devoted to the use of BCG will be subtracted from normal methods of prevention, *methods of which there is no doubt in terms of efficiency on any grounds by any person.*

It is stated that in some places so much money is being spent on the vaccination program that not enough remains for good case-finding and sanatorium work.

The International Tuberculosis Campaign was organized in 1948 by the United Nations International Children's Emergency Fund and three Scandinavian voluntary organizations—namely, Danish Red Cross, Norwegian Relief for Europe and Swedish Red Cross. This organization was set up in collaboration with the World Health Organization to promote and direct large scale BCG vaccination programs. By December 1, 1950, 30 million children and young adults had been tested with tuberculin; the nonreactors (approximately one-half) received BCG in the many countries involved in this campaign. The Czechoslovakian report[155c] revealed that the objective was to reach all persons between the ages of 1 and 20 years. At the height of this campaign, 46 teams with 260 persons were engaged in finding those who did not react to tuberculin and in giving them BCG. About 86 per cent of all nonreactors accepted BCG. Obviously for the most part these were children and young adults from homes where tuberculosis did not exist. The cost of this campaign was $306,514.91. A mass BCG campaign was conducted in Poland in 1948 and 1949[155d] in the same manner as that in Czechoslovakia, at a cost of $638,672.27. Much tuberculin testing and retesting of the so-called vaccinated individuals will necessitate large expenditures.

These are only two of many countries which were chosen for such mass BCG programs. Apparently these are not controlled experiments in any sense. If comparisons are attempted they will be on unlike groups. Inasmuch as all nonreactors to tuberculin who could be reached or who accepted BCG received it, there remain no other groups except those who originally reacted to tuberculin and did not receive BCG. Obviously those who received BCG had not had effective contact with contagious cases of tuberculosis at home or elsewhere and therefore they were not potential cases of clinical tuberculosis at that time. On the other hand, those who did not receive BCG by virtue of being tuberculin reactors already had at least primary tuberculous lesions in their bodies and probably many of them were frequently being reinfected from their original infectors. Thus they were potential cases of clinical tuberculosis throughout their lives.

Again, since tuberculosis is decreasing in so many parts of the world, it will be impossible to determine whether decreases which occur in countries with mass BCG programs are due to this organism or to other factors.

Dubos and Dubos[155e] call attention to a current example, as follows:

> Many attempts have been made to produce immunity by using for vaccination living bacilli totally devoid of virulence for man. A culture isolated from a water turtle was widely promoted for this purpose under the name of "Friedman vaccine" half a century ago. Although all evidence shows that it has no anti-tuberculous activity whatever, it is still being produced commercially in several parts of the world. So vigorous is the life instilled into useless medicines by human hopes and gullibility!

Persons from nations which have done little to control tuberculosis often state that if the disease were at as low levels as it is in some areas and countries they would give BCG no consideration, but with their present tremendous problems they feel that vaccination should be tried. This would appear to be only postponing the day when they must develop fundamental programs and practice the same procedures as the low level countries to which they refer have done for the past 25 to 50 years. To date there is no evidence that BCG or any other so-called vaccine has ever reduced the tuberculosis problem in any nation.

Incompatible with Fundamental Work

BCG sensitizes tissues to tuberculoprotein and thus nullifies subsequent use of the tuberculin test. This is a tremendous loss to a tuberculosis control program anywhere, since the tuberculin test is the finest of all diagnostic, epidemiologic and control-measuring agents. BCG does not protect against subsequent infection with virulent tubercle bacilli, but denies its recipients and their physicians the right of knowing if and when virulent tubercle bacilli invade their bodies. Thus, those who do become infected are not alerted for subsequent dangers and the sources of their virulent infections are not sought. To sensitize tissues of people to tuberculoprotein with BCG or any other so-called vaccine may be likened to discarding serologic tests for syphilis and waiting for paresis, tabes dorsalis, aortitis, etc. to manifest themselves before instituting treatment.

Whenever a preparation becomes available that will destroy all tubercle bacilli in the human body, it will serve its best purpose if it is administered as promptly as possible after the first invasion with tubercle bacilli occurs. This time can be determined only by the tuberculin reaction, which becomes manifest within eight weeks after the invasion occurs. Such prompt detection and treatment will be denied those who have had BCG, because the invasion of their bodies with virulent tubercle bacilli cannot be detected by the tuberculin test.

A considerable number of persons who have received BCG have fallen ill some time later and some have died. If this is not due to BCG itself, it would seem likely that they became infected with virulent organisms following the so-called vaccination. My experience with persons who have received BCG is that they have such a false sense of security that they see no need for periodic examinations; thus, those destined to develop clinical tuberculosis are likely to go along blindly until symptoms appear, when the disease is in an advanced stage.

A few persons have recommended that BCG be used as an adjunct to the fundamental tuberculosis eradication program. To do so, however, is ruinous to the fundamental program inasmuch as it nullifies the valuable tuberculin test, gives the public a false sense of security and results in reduced cooperation in the tuberculosis control program.

Concerning BCG, Wilson,[97] in what he calls public health anachronisms, refers to "practices that are carried on now because they have been in use for the last 30 years or so, even though it has since been shown that they are of little or no value for the purpose for which they were originally intended. The accumulated weight of precedent is almost overpowering and I, therefore, ask you to pause a moment before committing yourselves to a practice that it may be very difficult subsequently to discontinue." This is an extremely important point with reference to therapeutic and so-called immunizing agents in tuberculosis. The literature abounds with examples of drugs such as creosote, gold salts, iodine and tuberculin which were introduced on the basis of personal opinions and theoretical considerations. Although they have

been found of no value in the treatment of tuberculosis, they are still prescribed by some physicians. Despite so little proof for efficacy and harmlessness of BCG, if it were recommended for general use or even among so-called contact groups, in all probability it would be employed by some physicians long after the futility of such a program is more generally recognized.

Concerning this "greatest mass immunization in history," Dubos and Dubos[155e] say:

> For reasons already discussed, it will probably never be possible to determine the effects of the Joint Enterprise on the course of tuberculosis in the countries where it operates. It is certain that the disease will not be eradicated by vaccination, and it is likely that tuberculosis will remain a grave problem even in vaccinated populations if economic difficulties and social disturbances continue to interfere with general well being.

Fundamental Methods Supported

Although numerous articles have appeared in medical journals, lay magazines, newspapers, etc. containing unqualified statements concerning efficacy and harmlessness of various so-called immunizing agents, including BCG, it is of particular significance that the vast majority of physicians—including students of tuberculosis as a disease—have never become greatly concerned. Their fundamental training and experience do not permit them to indulge in procedures based on speculations, theories and personal opinions. On the other hand, the same fundamental training and experience cause them to immediately accept scientific and sound practical methods and procedures whose safety and efficacy have been thoroughly proved—witness immunization in smallpox and typhoid fever, insulin in diabetes and roentgen ray in diagnosis.

It is just such physicians who have protected and who continue to protect the public against unproved and possibly dangerous procedures by calling attention to their inadequacies. For example, concerning attempts to produce immunity in tuberculosis—particularly those of Von Behring and Calmette—Wolff[156] said:

> These attempts were unsuccessful as would be expected in a disease the course of which is as slow as that of tuberculosis in man, and thereby show that in the majority of cases natural infection does not produce an enduring immunity. This is the sharpest contrast to such cases as that of smallpox.
>
> We can only repeat the words of Neufeld that one is assuming a phantom if one seeks to regard immunity against tuberculosis as in the same category of ideas as immunity against smallpox. Immunity in tuberculosis, in the sense of the classical antibody theories, does not exist.

> Though a presumptive case for the value of BCG vaccination has been established, it is concluded that the documentary evidence so far available is insufficient to allow any estimate to be made of the degree of protection it affords or even to prove conclusively that, in a civilized population, it has any protective effect at all. *(Wilson, 1947.[97])*

> It is essential to keep in mind that this relatively nonpathogenic strain had its origin from a highly pathogenic bovine type of tubercle bacillus, and that, until such time as the factors governing the pathogenicity of tubercle bacilli are known, BCG vaccine must not be considered as a virus fixé.
>
> Tuberculosis cannot be effectively controlled until the problem of tuberculous reinfection has been met and it is because of this situation that prophylactic vaccination against tuberculosis as now advocated would seem to be a rather puny weapon. . . . it is extremely doubtful that artificial vaccination can produce results superior to natural vaccination with small numbers of living virulent tubercle bacilli and yet natural vaccination fails to control the disease. It appears illogical to base a major attack against any disease on a skirmish against a minor phase of the problem. (This is asking the tail to wag the dog.) . . . One need not disagree with the concept of vaccination as a procedure to hold that an effective control of tuberculosis cannot be obtained without a major attack on the source from which the disease is spread. The present program of mass vaccination with BCG does not touch this problem and it would appear illogical to anticipate that artificial vaccination could succeed where natural vaccination has failed. *(Medlar, 1949.[157])*

> First, it must be admitted in clear and unequivocal terms that strict scientific proof of the effectiveness of BCG vaccination in the control of human tuberculosis is not available. *(Palmer, 1949.[158])*

> It is even conceivable that many of the classes of human beings who are most dangerously exposed to tuberculosis (for example, those living under conditions of great economic stress with inadequate food supplies) may be those least capable of responding satisfactorily to immunization procedures. *(Dubos, 1949.[114])*

> Tuberculosis can be entirely eliminated, and has been in certain areas, by tuberculin testing, x-raying reactors, and isolation of open cases. BCG would interfere with such programs and might add the danger of large numbers of subclinical tuberculosis among the population at large. Any favorable report of BCG vaccination can be surpassed with reports with the use of accepted methods. *(Dickey, 1950.[159])*

We have before us examples in at least two countries where BCG vaccination has been carried on for many years, yet where no scientifically reliable data can now be obtained as to what part BCG vaccination has played in the history of tuberculosis in the country as a whole.

We cannot give unqualified credence to the belief that a general or decided decline in tuberculosis morbidity in France or Denmark or any other country where BCG has been used constitutes evidence that BCG vaccination was effective. *(Anderson and Palmer, 1950.[110])*

Tuberculosis cannot be eliminated from the United States by BCG vaccination, regardless of how efficiently it is applied. The only sure way to eliminate the disease is to practice what we have been preaching for the past 50 years. Every individual with active tuberculosis must be detected, isolated and treated until he is no longer infectious. *(Smith, 1950.[160])*

BCG vaccine has been used on humans since 1921, yet we do not know whether it is effective and, if so, how effective. *(Todd, 1950.[161])*

After producing progressive and fatal tuberculosis with BCG in silicotic guinea pigs, Vorwald, et al.[109] said:

In the light of the findings in this investigation, the statement of the adherents of BCG vaccination that the BCG organism is a stable strain or *virus fixé* must be reconsidered (1950).

Vaccination with BCG organisms does not prevent or retard the development of tuberculosilicosis produced by an infection with the attenuated R_1 strain of the human type tubercle bacillus in the presence of inhaled quartz dust. *(Vorwald, et al., 1950.[109])*

It must be recognized and admitted, however, that we have a woefully incomplete knowledge of just what it is that is being used as BCG. *(Anderson and Palmer, 1950.[110])*

BCG, the vaccine now being exploited, is only one of a long series of such vaccines starting before the turn of the century. There has been enthusiasm for all of them. Somehow, despite the similarity of claims for each of these vaccines, one by one they have disappeared from public notice and from scientific recognition, only to be followed by another very similar product. Either the desire for a vaccine is very great, or we are hard to convince. . . . It would seem that the most cursory examination of the facts as they actually exist (would indicate) that the hope of eliminating tuberculosis by vaccination is a vain one. It would seem that we are likely to increase the disease rather than eradicate it, if we vaccinate large masses of children. *(Levine, 1951.[168])*

Unfortunately, tuberculosis, unlike the diseases mentioned above, induces little if any immunity. Indeed, as everyone knows, the patient who has recovered from clinical tuberculosis is even more likely to have a second attack than an individual who has never had the disease. Therefore, one cannot expect very much immunity from BCG vaccination. It is unfortunate that the technical term "vaccine" was ever applied to the BCG product since it implies to the public that it is as effective as smallpox or typhoid vaccination. *(Smith, 1951.[15])*

It would appear that considerable further knowledge is needed before this vaccine can be accepted as a general public health measure in the United States or even licensed for production by commercial laboratories.

No method has been developed for stabilizing the potency of the vaccine. No means has been developed to assure that similar amounts of BCG from different laboratories would have equal numbers of viable organisms and equal potency. We still have no knowledge of the actual degree of immunity conferred by the vaccine, or the duration of this immunity. We are not agreed on the optimal dosage to be given or the best method of administering the vaccine. *(Levine, 1952.[163])*

It is also disturbing to find that the virulence of BCG strains is not constant and that in certain circumstances, e.g., when animals are maintained on deficient diets, the BCG used for immunization can cause pulmonary disease and even death. The harmlessness of BCG vaccine has by no means been established.

These observations are alarming. Coupled with the fact that recent work in France has demonstrated the capacity of BCG vaccine to produce a widely disseminated killing disease in apparently normal hamsters. . . . *(Shapiro, 1952.[163a])*

Concerning BCG, Farber [163b] wrote:

So far as I am concerned, the most disturbing evidence of all is the plain fact that after 40 years its effectiveness is still a matter for debate. Every major study of its positive contribution to tuberculosis control is open to serious objection. Even among its proponents, there is little agreement as to what, exactly, is to be gained by its use. If there were only a question of the amount, duration and consistency of the immunity this vaccine confers, it would be open to objection. As a matter of fact, however, there is no way of demonstrating any immunity at all resulting from its use, except by controversial statistics.

Marshall[155a] said:

The present story of BCG follows a gradual transition in use from oral feeding of exceedingly young infants to the inoculation of adults, a transition which is hard to trace in science or in fact but which has certainly in part been the result of wishes and frustrations.

Given to adults, inevitably some will receive BCG superimposed on some stage of infection, essentially a febrile inoculation with a lethal agent capable of stirring up latent infection. Nearly all such cases are written off, statistically, as mere failures of BCG, not attributable to it. The ethics of sacrificing 8 to save 10 or 1 to save 10 should not be open to debate.

Conclusions perhaps can be drawn from existing data, but they are against the use of BCG and not in its favor. We might say that a pilot experiment is unwise in the sense that we should now either believe in BCG or have the courage to say "no" to it. In my mind the vote would be "no" to both pilot experiment and the acceptance of BCG.

The arguments used in favor of BCG are tinged with hope and wishes. True, the tragedies of tuberculosis might warrant risks which otherwise would not be warranted, but these tragedies have nothing to do with the success or failure of the product. The acceptance of BCG by others is no argument, for these others are not omniscient. The fact that reputable men who have reviewed the evidence stand on two sides is ample evidence that neither side is sure of its ground. In this instance, the risky side is the side of the proponents, for they are in a position to be governed by potent wishes whereas antagonists are obliged to go against their hopes, sympathies, and, assuming that there are instances in which BCG can be of value and knowing that, true or not, this will be charged by anyone who has been denied BCG and develops a clinical case, against their social status and political good will. Proponents will not be blamed for trying, even with danger. Antagonists will be blamed for honesty, even though right.

Torning[145a] (Copenhagen), referring to mass x-ray surveys and "vaccination" programs by touring teams, stated:

But it would be a catastrophe if such measures created in the minds of general practitioners the feeling that tuberculosis is something which others take care of. The practitioner deals with sick people and tuberculosis is more common among people who feel ill than among those who feel well. He is the man who first sees the sick person and who knows his environment. Therefore the tuberculosis minded general practitioner is the cornerstone in the fight against tuberculosis.

All tuberculosis workers must be deeply impressed with the remarkable uniformity of results of the dozens of attempts to produce immunity in animals and humans by the use of living tubercle bacilli of both human and bovine types after they have been reduced in virulence, as well as with the almost identical results from use of tubercle bacilli of both types after they have been killed by various methods. Most of these preparations, both living and dead, appeared to result in considerable immunity—so much that those who produced them often manifested enthusiasm and strongly recommended them as a practical method of controlling and eradicating tuberculosis.

Always, the enthusiasm expressed for numerous "immunizing agents" was due to observation of too short duration or to a lack of understanding of the phenomenon involved. In every instance when animals thought to be immunized were kept under observation sufficiently long, they died from tuberculosis caused by virulent organisms against which they were believed to be protected. Hence one "immunizing agent" after another had to be discarded for lack of efficacy.

The earlier workers had no understanding of allergy. Not until later was it learned that hypersensitivity of tissues to tuberculoprotein causes them to react specifically and intensely to reinfections with tubercle bacilli, thus temporarily fixing the organisms at their points of focalization. Although held for a time at these sites, the defense mechanism does not have the ability to destroy the tubercle bacilli and often not even to prevent their multiplication. Therefore, at these fixed areas colonies develop from which tuberculoprotein is eliminated to kill adjacent cells and tissues with resulting small or large areas of necrosis. From these areas tubercle bacilli may later spread to adjacent tissues and even to remote parts of the body to set up new lesions.

Another fact for serious thought is that, beginning in the 1880's and '90's and continuing to the present, many physicians have warned against introducing into human bodies living virulent tubercle bacilli that have been attenuated in virulence. This frequent warning has not been without cause, since it is well known that virulence of tubercle bacilli may be regained. Even when kept in laboratory cultures, forms appear, probably through mutation, which have much greater ability to multiply in vivo than the original. There can be little doubt that in the early 1920's, BCG cultures consisted of a single bacterial form which did not produce tubercles in animal tissues, but after more than a quarter of a century of life in culture mediums, significant changes have occurred—so significant, in fact, that no one knows the composition of cultures now in use. They have not only caused progressive and killing disease in three species of laboratory animals but also frequently resulted in clinical tuberculosis at the site of administration and in the regional lymph nodes in humans. In the many persons who have fallen ill and the considerable number who have died subsequent to "vaccination," almost no work has been done to determine whether one of the bacterial forms now present in BCG was responsible. Therefore

there is little wonder that so many physicians are still warning against introducing into humans living tubercle bacilli under the name vaccine.

Tuberculosis workers everywhere must also be impressed with the conclusions reached by students of tuberculosis in the 1880's to the effect that tuberculosis differs from such diseases as smallpox, typhoid fever and diphtheria in that an attack of this disease with microscopic or gross lesions does not result in dependable immunity. This same conclusion has been drawn and emphasized by numerous students of tuberculosis through the subsequent decades to the present time and thus attention frequently has been called to the futility of attempts to produce immunity artificially.

No informed physician can fail to appreciate that tubercularization of a family, a nation or a race of people has never solved the tuberculosis problem. Invariably such perpetuation of tubercle bacilli has only augmented the problem. If it were not so, one would not now see clinical tuberculosis in epidemic form in nations where tubercularization apparently has been well nigh complete for centuries.

There is no dependable immunizing agent for leprosy, yet by the end of the sixteenth century—long before the bacillus of leprosy was discovered—this disease was eradicated from England and most of Western Europe. This was accomplished by providing leprosariums on a large scale, with at least 20,000 in Western Europe and more than 200 in England. The method consisted of isolating persons with contagious disease so as to prevent others from becoming infected. Concerning this, Smith[160] said: "The detection and isolation of lepers was carried out with a thoroughness which has never been approached by our campaign for the detection of the open case of tuberculosis."

By the same method, tuberculosis has been controlled among children[154,164] and among students of nursing[165] and of medicine[166] far more successfully than has ever been reported by the use of any so-called immunizing agent. By this method tuberculosis has actually been eradicated from children of school age in sizeable areas (Figure 10) and has been reduced to a minor problem among young adults. This method permits no theory, speculation or personal opinion. It has been demonstrated and proved beyond doubt as the only method now known by which the medical profession and its allies can eradicate tuberculosis. Those promoting methods for eradication of tuberculosis are at the same time eliminating the tubercle bacillus of any degree of virulence. They strongly oppose the use of a living so-called vaccine such as BCG, which harbors, protects, nurtures and perpetuates tubercle bacilli.

Although dependable immunity in tuberculosis has never been demonstrated and there is no evidence that it exists or can be produced artificially, the ever-continuing search for immunity in tuberculosis continues.

Summary

25. As evidence accrued concerning the danger of introducing into humans living tubercle bacilli thought to be attenuated in virulence, many workers—recognizing the probable danger ahead—have recently advocated the use of only dead tubercle bacilli as vaccine. Thus, preparations have been made from virulent human type and vole tubercle bacilli killed by ultraviolet light, as well as from dead BCG. These make the tissues of animals allergic to tuberculoprotein to approximately the same degree as live BCG. This is a revival of methods used in the latter part of the nineteenth and the early part of the twentieth century, with the same result. It is deceiving workers of today just as it did those of earlier periods. Although vaccine made from dead tubercle bacilli avoids the danger of causing progressive tuberculosis, there is no proof that it provides dependable immunity.

26. Paradoxically, allergy is now used as a criterion of presence of immunity. When an animal or a person has received a so-called vaccine made from either living or dead tubercle bacilli and allergy is demonstrated by the tuberculin reaction, immunity is said to have been established. As yet, no satis-

factory evidence has been presented to show that allergy has anything to do with immunity. The tuberculin reaction now being used as a criterion for the presence of immunity is only a test for hypersensitivity of tissues to tuberculoprotein.

27. Allergy is usually a prerequisite to the development of clinical tuberculosis; therefore to produce allergy artificially is to set the stage for this type of disease if and when virulent tubercle bacilli invade the tissues.

28. Accomplishments by standard methods are now being credited to so-called immunizing agents. In areas including nations where BCG has been extensively used, mortality rates have not decreased more than in other places where no so-called immunizing agent has been employed. If an immunizing agent were effective, it should first be reflected in reduced morbidity, but in areas where BCG has been extensively used there is no evidence of corresponding reduction in morbidity that is not explainable as resulting from other factors. The most marked decreases in tuberculosis mortality have occurred in areas and nations where BCG has not been used. In such places there is every reason to believe that the reduction in tuberculosis has been due to education resulting in early case-finding, isolation and treatment in hospitals and sanatoriums, and control of tuberculosis in animals.

29. The present propaganda for so-called immunizing agents presents a serious threat to the most successful tuberculosis control program of all time. Persons found to have contagious tuberculosis and some now institutionalized for this disease are asking that they be permitted to remain in or return to their homes because they have "learned" that their children and other associates can be vaccinated against tuberculosis as is done against smallpox. Legislators are asking why funds should be requested for the building of new sanatoriums and additions to and repairs of others, since they have been given the impression that sanatoriums will not long be necessary because of vaccination. People are asking why there should be a tuberculosis Christmas Seal sale, since they believe vaccination will soon make such organizations as the National Tuberculosis Association and its 3000 component societies unnecessary.

30. The tuberculin test is the finest of all diagnostic, epidemiologic and control-measuring agents. Administration of BCG, vole tubercle bacilli or dead organisms nullifies the subsequent use of the tuberculin test to determine whether and when virulent forms of tubercle bacilli enter the body. Thus the individual is denied the inalienable right to know if and when this significant event occurs. If a drug is found that will destroy tubercle bacilli in human tissues, it will be most effective when administered promptly after first invasion with virulent tubercle bacilli. The early presence of such invasion can be determined only by the tuberculin test. Such prompt detection and efficacious treatment will be denied those who have previously had BCG.

31. No present day so-called immunizing agent can be used as an adjunct to the fundamental tuberculosis eradication program. These agents not only destroy the value of the tuberculin test but also give the public a false sense of security.

32. Although so much is now being said about efficacy and harmlessness of so-called immunizing agents that those who have become overzealous about them are risking great names, it appears that the majority of physicians have not lost their poise. Their fundamental training and experience do not permit speculations, theories and personal opinions in matters so important as the eradication of man's greatest scourge. On the other hand, the same training and experience cause them to approve and enthusiastically support methods and procedures with thoroughly proved safety and efficacy such as immunization for smallpox and typhoid fever, insulin for diabetes and roentgen ray in diagnosis.

References cited in this and the two preceding parts of Dr. Myers' article will be included in the author's reprints.

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DEVELOPMENTS IN DIABETES DETECTION

EXPERIENCE gained in conducting the four previous Diabetes Detection Drives enables us to look forward confidently to the fifth, which takes place during Diabetes Week, November 16 to 22, when the annual case-finding and health education program sponsored by the American Diabetes Association will be renewed throughout the country. It will be carried out by the medical profession working through state and county medical societies and affiliate diabetes associations in over 700 areas in the United States, Canada, Hawaii and Puerto Rico.

This series of screening programs, designed to help find the estimated 1,000,000 Americans who have diabetes and who do not know it, has been valuable as a health educational program, as a large scale testing project and as a reminder to wayward patients to return to their doctors for more consistent treatment and stricter control of their diabetes.

Methods of diabetes detection have been improved considerably in recent years, so that it is now possible to make simple and inexpensive tests available to great numbers of people. The medical awareness of the prevalence of the disease is so widespread nowadays that fairly accurate estimates can be made of the number of potential and hidden diabetics in various areas.

This is in great part due to the activities of the American Diabetes Association, whose work throughout the year is highlighted by Diabetes Week, when posters and mass distribution pamphlets bring a consciousness of the problem of diabetes to large sectors of our people.

In addition to this public information, the association makes available testing material to medical groups cooperating with the civic, business and community organizations participating in the Diabetes Detection Drive, as well as the 31 local diabetes associations, consisting of both medical and lay groups, who bring the message of diabetes detection to all stratums in their communities.

Regardless of the screening methods used, however, the educational campaign of the association emphasizes *that the diagnosis rests with the physician*, and that such diagnosis can be made only after a thorough physical examination and follow-up studies.

An integral part of the public information broadcast during Diabetes Week is the emphasis on the necessity of continuous teamwork by both the physician and the diabetic patient. The physician, in addition to diagnosing and prescribing treatment for the new diabetic, must also prepare the patient to live with his disease for the rest of his life. Continued management is necessary since the requirements of the patient change through the years that follow.

In assisting both the doctor and the diabetic patient to keep up to date with the developments in the field of diabetes research and treatment, the association issues two magazines. One, *Diabetes*, is a scientific journal available to the profession. It contains the latest clinical and research findings in the field, a large section being devoted to Diabetes Abstracts and articles concerning experience in treatment. A lay magazine, the *A.D.A. Forecast*, is also issued bimonthly for diabetic patients. Written in popular language, it contains suitable information on diabetes and its complications, diet suggestions and menus, and personal communications from diabetics on their experiences in the successful management of their ailment. It emphasizes the positive values of consistent diabetic control and furnishes a wide range of useful information for the diabetic patient and those who care for him.

In addition the association provides answers to queries from the public on the subject of diabetes and its many facets.

Through posters and literature of a positive tone, the public is made aware of the fact that diabetes, if detected early and treated properly, seldom interferes with normal active living. By publicizing well known personalities who have achieved prominence in their chosen fields, the association offers new diabetics living evidence that with proper treatment he or she can live successfully.

It is also pointed out that diabetes—if not detected in time—may become a crippling illness.

Since diabetes is a chronic disease for which there is a known control, the big task is to find the unknown diabetic quickly, and to educate him or her on how modern medicine can control this ailment. At the same time, diabetic patients who have strayed from their regimen are reminded of the necessity of continuous control and a return to their own physicians for a check-up.

As the number of medical organizations cooperating in the annual Diabetes Detection Drive increases each year, the goal of this educational program comes nearer. The search for the estimated 1,000,000 unknown diabetics will continue, according to the association's plans, until every man, woman and child has a *periodic* health examination by his own physician—an examination which includes a test for diabetes.

JOHN A. REED, M.D.
Chairman, Committee on Detection and Education and Secretary American Diabetes Association, Inc.

INTERNATIONAL CONGRESS ON MEDICAL EDUCATION

RECENTLY in Brussels the organizing committee of the jointly sponsored International Congress on Medical Education, which has the support of the World Health Organization and of the World Medical Association, met to develop further plans for the first and no doubt epoch-making meeting in the field concerned. The chairman of the organizing committee is Dr. T. C. Routley, secretary of the Canadian Medical Association and a member of the Council of the World Medical Association.

The president of the First International Congress on Medical Education is Sir Henry Cohen of England, widely known for his championship of the general practitioner in the various controversies that have arisen in Great Britain under the National Health Act. The headquarters will be in the offices of the British Medical Association, and Mr. Harold Edwards is the general secretary assigned to handle the detail of the congress. The chairman of the committee on arrangements is Dr. Rowland Hill. Other members of the British Medical Association are participating in considerable numbers in order to assure the success of this great occasion. Honorary vice presidents representing other sections of the world will preside over the various sections of the First International Congress, and it is estimated that from 80 to 100 distinguished medical educators will participate in the sessions. Obviously hundreds of other physicians and medical educators will attend as observers and take part in the general discussions.

The special problems of medical education to be considered concern the preliminary edu-

cation of young men and women who are going to enter the study of medicine, the manner of selection of the medical students, the aims and content of the curriculum and the study of social medicine and its application to the practice of medicine. Tentatively planned also for this important congress will be a great exhibit designed to make available to physicians all of the newer technics used in medical education, including motion pictures, television, practical technics involved in cardiology, roentgenology and pathology, as well as the latest works developed by medical publishers throughout the world. Indeed every possible method used in the education of physicians will be given opportunity to display its products and their results.

The International Congress will meet in London, August 24 to 29, 1953. The meeting will be followed by the meeting of the World Medical Association which is to take place in Amsterdam. Many other important international congresses are scheduled for Europe in 1953. No doubt thousands of American physicians will find it worth the time, the effort and the money to make the trip abroad and to participate in these important scientific assemblages.

MORRIS FISHBEIN

POSTMORTEM BACTERIOLOGY

In 1934 Burn[1] investigated the danger of bacteria found post mortem. He reported that *Bacillus coli*, *Staphylococcus*, nonhemolytic streptococci, *Streptococcus viridans*, *B. welchii*, diphtheroid and *Proteus* types are the most frequently isolated strains of bacteria. Other bacteria isolated post mortem are usually associated with the diseases from which the persons died. Burn said that the most frequently isolated types are the usual inhabitants of the respiratory and intestinal tracts. Those less frequently found are usually present in association with some infectious condition. The mode of entrance of bacteria into the dead body is by way of the lungs, kidneys, liver, spleen and blood. Burn failed to find significant differences in the frequency or the kind of bacteria isolated from the organs post mortem between the first and the forty-eighth hour after death. Glaister[2] reports that the bodies of chronic alcoholics and those of persons who have died by poisoning from such substances as carbolic acid, arsenic, antimony and zinc chloride resist putrefaction longer owing to the preservative action of these chemicals on the tissue or to their destructive or inhibiting action on the growth of the organisms that cause decomposition of the body.

Weed of the section on bacteriology and Baggenstoss[3] of the section on pathologic anatomy in the Mayo Clinic have recently reported their studies of the isolation of pathogens from embalmed tissues. Previous studies have been concerned with specimens removed during surgery and have emphasized the importance of thorough bacteriologic examination of tissues removed surgically as a supplement to the usual histopathologic method which is used in securing an accurate etiologic diagnosis.

During the examination of embalmed bodies unexpected lesions are sometimes encountered which would be subjected to extensive bacteriologic studies on bodies that were unembalmed. Formaldehyde destroys bacteria rather rapidly. Most embalming fluids contain formaldehyde. Pathologists have felt that the micro-organisms in the tissues are usually rapidly destroyed by the embalming and therefore bacteriologic studies have not been done.

Now for some six years the investigators have been making bacteriologic studies of embalmed bodies and have been much surprised to find that in many cases organisms which appeared to be the cause of death could be isolated without difficulty and in pure culture from embalmed tissues. From various tissues and body fluids such commonly encountered organisms as *Escherichia coli*, *Klebsiella pneumoniae*, *Micrococcus pyogenes*, various species of *Streptococcus*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Hemophilus influenzae* have been isolated. Moreover, some important pathogens of more than casual importance to the pathol-

ogist have been secured, notably, *Nocardia asteroides* in 2 cases, *Histoplasma capsulatum* in 1 case and *Mycobacterium tuberculosis* in 22 cases. Special emphasis is attached to the isolation of the tubercle bacillus from 22 bodies and from several lesions in many of these bodies. In many cases the bodies had been embalmed for as long as 24 to 48 hours and in one case, 60 hours.

In their comment on their studies the Mayo Clinic scientists raise the question as to whether or not infections of pathologists with tuberculosis may have occurred from the handling of tissues from embalmed bodies under the erroneous assumption that all bacteria were dead. Since they were able to isolate virulent tubercle bacilli from the tissues of 22 out of 23 embalmed bodies in which there was sufficient evidence that viable organisms were present, they conclude that embalming, as ordinarily done by the arterial route, does not render the tissues free of contagion in a short time.

MORRIS FISHBEIN

1. Burn: J. Infect. Dis. 44:395, 1934.
2. Glaister, John: Medical Jurisprudence and Toxicology. Baltimore, Williams & Wilkins, 1942, p. 129.
3. Weed, Lyle A. and Baggenstoss, Archie H.: The isolation of pathogens from embalmed tissues. Proc. Staff Meet., Mayo Clin. 27:124 (March 26) 1952.

BARYTA AS A SUBSTITUTE FOR LEAD TO PROTECT AGAINST RADIATION

In Portugal the Instituto Portugues de Oncologia has a pavilion for radiation in which protection of technicians and patients against radiation effects of radium and x-rays is accomplished by the use of baryta instead of lead. The importation of lead from Spain would have been extraordinarily expensive. The idea, therefore, occurred to Professor F. Gentil to substitute baryta which is plentiful in the south of Portugal. Research was done which showed that a mixture of baryta and cement in the proportion of 9:1 provided a building material which was sufficiently resistant. Since the baryta was not pure, secondary radiation was avoided by placing a cork plate on each side of the baryta. Cork is also plentiful in Portugal. The width of the baryta plus cement in proportions of 9:1 was 16 cm. The width of plates of cork on each side of the baryta was 2.5 cm. each. This was shown by research to be equivalent to protection obtained by 4 cm. of lead. On each face of this material is reinforced concrete 7 cm., and the finishing material 2.5 cm.

A communication from Dr. Marshall Brucer, chairman of the Medical Division of the Oak Ridge Institute of Nuclear Studies, indicates that the impression has prevailed in this country that this method was developed during the investigations of the Manhattan District. It appears now that the idea was original with the Portuguese. Baryta is a barium monoxide ore. The recommendation is now made that various types of ore be used, depending on the section of the country. Thus marble and Virginia soapstone both have better radiation protection characteristics than does any of the barium monoxide ores or the high density concretes. Marble can be finished and used as a structural member without the necessity for complicated forms and plastering to get a finished surface. Notwithstanding the fact that this concept was introduced as early as 1934, at this very time hospitals are being built in various places in the United States in which concrete walls are filled with layers of lead at tremendous expense.

This observation is another indication of the importance of transmitting information in the field of medical science. The difficulty lies first in the great number of scientific periodicals printed in a variety of languages and more particularly in the unavailability of first class indexes with sufficient cross indexing to provide for easily finding the material. The failure of scientists to search the literature suitably in relationship to various phases of their work is apparent.

MORRIS FISHBEIN

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Your Questions answered

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• ELASTOSIS SENILIS

Question: I am very puzzled over the symptoms of one of my patients who has a case of precocious senile elastosis. This 42 year old woman has cataracts, difficulty in hearing, atrophic pelvic organs and marked senile changes of the skin. Would the term *elastosis senilis* fit this picture? I have searched the literature and whenever I find a report on a case of elastosis, it specifies senile, which does not fit the requirements in this case. What would be the cause of this apparent premature senility? Any information you can supply will be most gratefully appreciated.

M.D.—Maryland

ANSWER: It would seem that the term, "elastosis senilis," would fit the above description. The other possibility that comes to mind is that of Vogt-Koyanagi syndrome, several features of which, including poliosis and dysacousia, are lacking in the description provided.

The cause of such premature senility as that described is not known.

• MANAGEMENT OF DOUBTFUL CASE OF SYPHILIS

Question: A 26 year old woman entered this country from Germany to marry a G.I. whom she had met in that country. Several serologic examinations made prior to entry, and one at the time she left for this country, were reported as negative. On January 1952 a premarital serologic test was reported as follows: complement fixation test negative; Hinton test positive; Kahn test positive. Despite the absence of a positive history or findings, the patient was given 6,000,000 units of penicillin. In March 1952 a repeat examination was reported as follows: complement fixation test suspicious; Hinton test positive; Kahn test positive (less than 10 units). In June 1952 the report was: complement fixation test negative; Hinton test negative; Kahn test suspicious. The patient became pregnant in June. In August the laboratory reported: microslide precipitation test positive; Kolmer complement fixation test positive in 4 dilutions; Hinton test positive.

Should this patient receive further treatment and, if so, of what should the treatment consist?

M.D.—Rhode Island

ANSWER: It is impossible to make a diagnosis of syphilis based on the results of serologic tests alone, and particularly on conflicting results. The first step in the mismanagement of this case was that of giving her 6,000,000 units of penicillin in the absence of evidence that she had syphilis.

The fact that there have been changes or apparent changes in this woman's reagin titer does not mean that she herself has experienced these changes: This most likely means a change in the sensitivity of the tests performed. *Have all of these tests been performed in the same laboratory?* If so, this is a grave error. No laboratory or test is infallible. Does she have other illnesses which could be responsible for biologic false positive reactions? Had she been immunized to any diseases just prior to coming to this country, or has she been immunized since that time?

Have any attempts been made to discover a possible source of infection? What is the status of her husband? If she did not have syphilis, as is indicated, when she came to this country, but after coming here acquired it, then there should not have been any difficulty in making a positive diagnosis by making use of time, necessary clinical examinations, proper serologic testing and proper contact investigations.

If this patient has not been exposed to infectious syphilis since receiving the 6,000,000

(Continued on page A-28)

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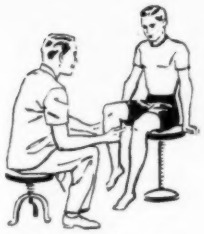

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units of penicillin, there is no need to give her any treatment during pregnancy. Reliable quantitative serologic tests should be performed once a month, and if the titer has a tendency to continue to behave as it has for the past several months, there is no need to give additional treatment. If the patient does have active syphilis, the reagin titer should rise and treatment then must be given. It has been shown that penicillin given during pregnancy will insure against syphilitic babies in virtually 98 to 100 per cent of cases. Therefore there is no need to take risks on having infants come into this world with syphilis. If there is doubt that a woman has syphilis, it is best to give her treatment during pregnancy and thereby be assured of a non-syphilitic baby. In the meantime, proper investigations may reveal whether or not the person might have syphilis.

After delivery, this baby must be investigated for syphilis by means of physical examinations, x-ray studies of long bones and monthly serologic tests for a period of four to six months.

LEE J. ALEXANDER

• BILIARY COLIC

Question: A 35 year old woman has persistent abdominal discomfort which began two years ago during pregnancy. Cholecystographic studies show numerous small calculi. She has had one attack of acute pain in the right upper quadrant. Is there any recommended treatment other than cholecystectomy?

M.D.—Iowa

ANSWER: It is wise in attempting to answer this woman's problem to make sure that no other disease is present to account for her abdominal discomfort and digestive symptoms. A gastric analysis and upper gastrointestinal series as well as a barium enema should be done before advising therapy. The fact that her symptoms began two years previously during pregnancy is strongly suggestive of biliary tract origin. In the presence of small calculi, in spite of the fact that she has had only one acute attack of pain, cholecystectomy should be strongly advised and done without delay. She probably will require exploration of the common duct at the time of cholecystectomy. Medical treatment in the presence of these findings is very unsatisfactory.

RICHARD B. CATTELL

• EMESIS FOR POISONING IN INFANTS

Question: We are confronted more and more frequently with incidents of accidental poisoning of babies with kerosene, drugs, washing solutions and other substances. What is the most dependable and safest method of emptying the stomach? Is apomorphine safe for infants? I dislike to use the stomach tube and it is often not feasible.

M.D.—New Jersey

ANSWER: Apomorphine is not safe for infants since their reactions to this drug are variable. Gastric lavage may be a lifesaving procedure and certainly is indicated when various drugs and poisons are ingested. It is by far the most dependable and safest method available.

However, the contraindications to this procedure should be kept in mind. Lavage is contraindicated in the presence of convulsions and in those patients who are comatose. Aspiration pneumonia may follow due to depression of the cough reflex. No lavage is necessary after the ingestion of caustic alkali, since the small amount that is usually swallowed is rapidly neutralized by the acid gastric juice. Nor should lavage be used in kerosene poisoning because of the danger of aspiration.

Emetics, though time-honored, are too apt to cause aspiration of vomitus in the age group most frequently ingesting poisons.

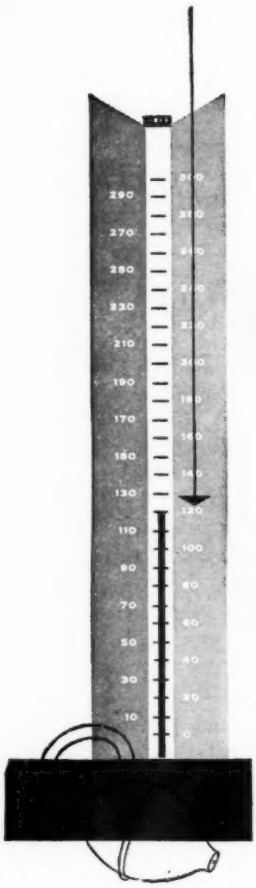
JAY M. ARENA

• AZOPYRIN

Question: I would like to inquire regarding a preparation called azopyrin. I would appreciate any information, literature and how to obtain this drug.

M.D.—Massachusetts

ANSWER: Azopyrin, now known as azulfidine, originally was prepared by Pharmacia Laboratories of Stockholm, Sweden, under the name of "salazopyrin." It is a combination of sulfapyridine and a salicylate. It has been particularly effective against some forms of arthritis and ulcerative colitis. It is now being used in ulcerative colitis with such complications as arthritis, pyoderma, uveitis and the like. It can be obtained from Medical Specialties, Inc., 300 First Street North East, Rochester, Minnesota.



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► THE TREATMENT OF DIABETES MELLITUS

By Elliott P. Joslin, M.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital, Boston. Co-authors: Howard F. Root, M.D., Priscilla White, M.D. and Alexander Marble, M.D. Ed. 9. 772 pages with 26 illustrations. 1952, Lea & Febiger, Philadelphia. $12.00.

This, the ninth edition of "The Treatment of Diabetes Mellitus," maintains the high standards of previous editions. With Drs. Howard F. Root, Priscilla White and Alexander Marble, Dr. Joslin has thoroughly revised all sections to include the latest information relative to the problem of diabetes. The title is misleading and an understatement. Besides a detailed and lucid presentation of therapy and management, all facets of the disease are considered. The introductory chapter, entitled "Present concepts of diabetes," is an excellent stimulus to further study, and by comparing the current status of diabetes with that of previous years the benefits to be gained by enlightened and painstaking care of the diabetic patient are emphasized.

Besides considering the incidence, etiology, pathology and physiology of diabetes itself, large portions of the text are devoted to the complications which lead to the vast majority of fatalities in diabetes. A major aim of the authors is to underline that proper control of diabetes is essential if the many complications are to be avoided or mitigated.

The juvenile diabetic and diabetes during pregnancy receive special attention in separate chapters written by Dr. White. The material in these sections, as in the others, is based to a large extent on the experiences of the authors with 34,000 diabetics treated at the New England Deaconess Hospital. Numerous pertinent references are cited. The appendix gives a new method of calculating diabetic diets and tables listing the composition of foods.

T. B. G.

► THE TREATMENT OF INJURIES TO THE NERVOUS SYSTEM

By Donald Munro, M.D., Surgeon-in-chief, Department of Neurosurgery, The Boston City Hospital. 284 pages with 47 figures. 1952, W. B. Saunders Company, Philadelphia & London. $7.50.

General surgeons and general practitioners who must care for patients with injuries of the central nervous system will find this book covers a great deal of territory, is concise, clear in its description and well organized. Because of the growth in the development of the specialty of neurosurgery many physicians have the attitude that there is no need to interest themselves in the different aspects of these conditions. The tendency is either to pass over lightly one's responsibility or to fail to carry out the proper procedures because of lack of knowledge and interest. This work places the responsibility squarely on the shoulders of those who see these patients initially and competently describes what should be done. While neurosurgical treatment is advocated wherever possible, it leaves no doubt that in the many instances where neurosurgical care is not immediately available the responsibility should be met by the physician or surgeon in attendance.

The opinions are dogmatic and give little choice. This is undoubtedly necessary in a treatise directed primarily to the general surgeon and general practitioner. There are, however, some instances where there may be some

(Continued on page A-52)

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difference of opinion. One of these appears in the discussion on aspiration of mucus from the oropharyngeal and laryngotracheal areas. The author leaves the impression that as a rule more harm than good is done in aspirating these secretions and possibly it is better to leave them alone than to do them inadequately. He also feels that tracheotomy is not justified and strongly condemns it except in special instances. There are other instances in which opinions may differ. They are of minor importance, however.

The section on the injury to the spinal cord is undoubtedly one of the best detailed accounts that one could obtain. The discussion of the care of the bladder and bowel is extremely clear and most worth while.

The operative descriptions are such that in an emergency a good general surgeon could follow them and do a satisfactory job. The limitations that should be felt by one not versed in neurosurgical technic are stated clearly. The author feels that these injuries should be taken care of by a neurosurgeon but includes operative descriptions and technics for those individuals who find that they must perform decompressions or laminectomies because of the emergency present or because of the inability to secure a proper neurosurgical consultation.

There is no doubt that this book will stimulate all who read it and will go far to dispel the old attitude that because a patient has an incurable injury to the nervous system the sooner he passes on the better. For this reason alone the book is a most worth while contribution to the medical profession.

W. P. R.

► CARDIAC PAIN

By Seymour H. Rinzler, M.D., Adjunct in Medicine and Cardiovascular Research Unit, Beth Israel Hospital, New York City. 139 pages, illustrated. 1951, Charles C Thomas, Springfield, Illinois. $3.75.

All the available knowledge of the cause and relief of cardiac pain has been compiled in this monograph. The author has very concisely summed up the mechanisms of production of cardiac pain from anatomic and physiologic standpoints, and has provided a pointed and instructive chapter on the differential diagnosis of chest pain in general.

The last part of the monograph is devoted to a discussion of therapy of cardiac pain and an excellent review of the current methods of medical therapy. Surgical therapy is thoroughly discussed and much space is devoted to the interruption of sensory pathways by paravertebral and local block, ganglionectomy and rhizotomy.

J. W. L.

► TOXEMIAS OF PREGNANCY

By William J. Dieckmann, M.D., Chairman, Department of Obstetrics and Gynecology, University of Chicago. Ed. 2. 710 pages with 85 text illustrations and 1 color plate. 1952, C. V. Mosby Company, St. Louis. $14.50.

Current knowledge about the toxemias of pregnancy is offered in this second edition of Dieckmann's monograph. The author has made the investigation of this subject his major scientific interest and as a result has become an international authority in his field. The new edition reviews literature reports of the past decade and includes the results of the investigations made by the author and his co-workers on the role of water balance and electrolyte changes in pregnancy and particularly as related to the toxemias.

The author points out in the preface that due to the slowing of research by the war there are few new facts which may lead to the solution of the etiology of eclampsia. Much more would be known about the subject if a concerted study were performed by a number of investigators with pooling of results. Despite these limitations the text exemplifies a good scientific monograph; i.e., it is a compendium of all the pertinent information about the subject and all its closely related fields.

The material is well indexed and contains a very adequate bibliography. There are many charts and tables to summarize results of investigative work and a number of photomicrographs to illustrate the section on pathology. Although the primary purpose of the text is to serve the obstetrician and the investigator untrained in obstetrics, any physician who is called on to treat the expectant mother will profit by access to the clinical information contained in the sections concerning prenatal care, treatment and prognosis.

M. B. S.

(Continued on page A-54)

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► PREVENTIVE MEDICINE AND PUBLIC HEALTH

By Wilson G. Smillie, M.D., Professor of Public Health and Preventive Medicine, Cornell University Medical College, New York. Ed. 2. 603 pages. 1952, The Macmillan Company, New York. $7.50.

This second edition is practically a new book, rewritten from beginning to end. The reviewer cannot think of a better book for the physician who would like to know something about the obligation he has to his patients and to his community to prevent illness and to promote health in the individual, the family and the community. This would be the best possible book for a physician who has just been appointed to a local health board and who must cope with problems of sanitation and the control of communicable diseases.

Covered in the text are such matters as the protection of water supplies and the sanitation of swimming pools, the disposal of excreta, food inspection and the sanitation of milk (section 2); epidemiology, control of the communicable diseases of childhood, of the enteric infections, of tuberculosis, of venereal disease, etc. (section 3); protection of children's health, school health services and prevention of accidents (section 4), and the protection and promotion of health in adults (section 5). There are also sections on mental hygiene, malnutrition, industrial hygiene and the prevention of other diseases.

The final portion of the book covers public health administration and the many problems that are handled by an administrator.

W. C. A.

► THE SKULL AND BRAIN ROENTGENOLOGICALLY CONSIDERED

By C. Wadsworth Schwartz, M.D. and Lois Cowan Collins, M.D., College of Physicians and Surgeons, Columbia University, New York. 386 pages with 335 figures. 1951, Charles C Thomas, Springfield, Illinois. $10.50.

Neuroradiology has become established as a subspecialty within the broader field of diagnostic roentgenology. Numerous specialists have developed in this field in the large medical centers around the country. However, the bulk of neuroradiologic lesions are observed by the practitioner of radiology whether he may be in a small community or in a larger city. The differentiation between the normal variants and the early significant lesions is often difficult; therefore it is important for this "general practitioner" of roentgenology to have as much source material as possible at his command.

This text discusses the technic of examination of the skull and the anatomy of the skull, together with practical consideration of anatomic variations and congenital anomalies. Of neoplastic diseases of the skull, examples of each condition are demonstrated. The most common conditions are more adequately illustrated than are the few more rare diseases. Discussion of brain tumors is centered about the classification of the tumor, and examples are given of the various lesions. The text detail covers the diagnostic criteria by which these lesions may be recognized. However, for the practicing neuroradiologist the subject is usually undertaken in a different manner. Confronted with the problem of identifying and localizing a lesion of the brain he analyzes the diagnostic criteria by the use of plain films, air studies and cerebral angiograms, and actually approaches the subject of differentiation from these examinations.

J. F.

► PRINCIPLES AND PRACTICE OF ANESTHESIOLOGY

By Vincent J. Collins, M.D., Director, Department of Anesthesiology, St. Vincent's Hospital, New York City. 528 pages with 99 illustrations. 1952, Lea & Febiger, Philadelphia. $10.00.

Teachers of anesthesiology long have felt the want of adequate textbooks and monographs for the average medical student, intern and resident. During World War I, the lack of adequate and organized material for the instruction of the young doctor going into the field of anesthesiology caused Dr. Arthur Guedel to write his classic monograph, "Inhalation Anesthesia, a Fundamental Guide." So it was that during World War II a more urgent and similar need arose. Those of us who are engaged in the instruction of the fundamentals of anesthesia to all kinds of personnel, both medical and nonmedical, are appreciative of the work which Dr. Collins has now presented.

The text is well organized and carefully written. It is presented along the lines of a classic

(Continued on page A-56)